TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK2820151 in Subjects with Advanced or Recurrent Solid Tumors

Compound Number: GSK2820151

Development Phase: I

Effective Date: 08-JUN-2017

Protocol Amendment Number: 04

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N215112_00	2014-DEC-15	Original
2014N215112_01	2015-JUN-19	Amendment No. 1
Amendment 1 includes, change in the Primary Medical Monitor, the clarification of Dose Escalation Schedules (Section 4.2) to make it clearer. Minor corrections in the summary of gastrointestinal risk. In light of emerging data from preclinical studies of embryo-fetal development, reproductive risk section, inclusion criterion #9 and guidance on contraception use were updated. List of prohibited and permitted medicines has been revised. Added more clarity on study termination criteria and greater flexibility on W3D4 PK samples window period. Statement on pregnancy follow-up inserted. Reference list updated.		
2014N215112_02	2015-OCT-06	Amendment No. 2
Amendment 2 is mainly in response to Food and Drug Administration (FDA) request and includes: changes in the Medical Monitors; modified the inclusion criteria and other relevant parts of the protocol to allow only patients with histologically or cytologically confirmed solid malignancy that is either metastatic or unresectable; revised hematologic Dose-limiting toxicity (DLT) definition for platelets which now also include Grade 3 thrombocytopenia with clinically significant bleeding in addition to Grade 4 thrombocytopenia (platelets <25,000/mm^3); added in the Dose Stopping Safety Criteria to permanently discontinue the patients from GSK2820151 who experience symptomatic (symptoms consistent with acute coronary syndrome) troponin elevation. Also, included an interim analysis for futility and safety review when 20 patients would have been recruited at the RP2D. Added clarification around collection of blood sample for pharmacokinetics (Section 8.4.1)		
2014N215112_03	2016-MAY-23	Amendment No. 3
Amendment 3 includes Inclusion criterion # 3 has been amended to allow the subjects who had progressed >3 prior line therapies. Exclusion criterion # 2 has been deleted to lift the restriction of 3 prior lines of cytotoxic therapy. MUGA Scan that had been stated as a second optional method for the measurement of ejection fraction has been removed from inclusion criterion #7. Clarification was made on the collection time for screening holter monitoring in Section 8.3.7. It was not intended to have holter required at Day-1 but rather performed within the 14 day screening window as outlined in the T/E table. Also, time points for holter monitoring were matched with triplicate ECGs time points. Time & Events Table was		

GlaxoSmithKline Document Number	**Date**	**Version**
updated to reflect the same. Minor correction made on AEs and SAEs reporting period in Section 9.2. Added more clarity on pain assessment which will be performed using Wong-Baker Faces Pain Rating scale. Appendix 11: Wong-Baker Faces Pain Rating scale added. A clarification on the collection and processing of safety cytokines, PK and protein biomarker samples process was made in Time & Events Table. Section 7.1.2.2, typo corrected "Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the **screening** visit through the post-study follow-up visit."		
2014N215112_04	2017-JUN-08	Amendment No. 4
Amendment 4 applies to all sites. Updates were made throughout the protocol to correct minor inconsistencies, spelling errors and provide further clarification. Salient changes include: • GSK Medical Monitor change • 4.6.1 Risk Assessment to include current available data • 5.1 Inclusion Criteria: update to contraception use in Inclusion 9 and 10 • Changes made in Exclusion Criteria Section 5.2 o clarification made on prior therapy (exclusion criterion-2) and anticoagulation use (exclusion criterion-3) o added to exclusion criterion-4 restricted use of NSAIDs and aspirin o updated exclusion criterion-13 to include history of bleeding and added known bleeding disorders • update to Section 7.1 Prohibited Medication and Non-Drug Therapies: o guidance on the use of exclusionary medications o prohibited & cautionary medication tables updated • Contraception requirements updated in Section 7.3 Lifestyle Restrictions • Corrections made in Time & Events Table 8.1		

GlaxoSmithKline Document Number	**Date**	**Version**

- addition of triplicate ECG on W1D2
- clarification around Pulmonary Function Tests
- Correction made in Table 8 Time and Events: Laboratory Assessments
- addition of Factor VII assay testing

- Added more clarity to troponin sample collection (Section 8.3.10 Troponin Measurement) and urine PK sample collection (Section 8.4.2 Urine Sample Collection for Pharmacokinetics)
- Appendix 7: dose adjustment/stopping safety criteria updated for QTcF, troponin, LVEF, hypo & hyperglycemia, diarrhea, mucositis, pneumonitis and thrombocytopenia toxicities.
- Appendix 12: NYHA Functional Classification System for Heart Failure Added

SPONSOR SIGNATORY:

PPD

Christopher Carpenter, MD, PhD
SVP, Head Cancer Epigenetics DPU, Oncology R&D

8 June 2017
Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After Hours Contact Information	Site Address
Primary Medical Monitor	PPD MBBS, MBA, MSc	PPD		GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom
Secondary Medical Monitor	PPD MD, MPH			ICON Clinical Research LLC 2100 Pennbrook Parkway North Wales, PA United States, 19454

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): 124949

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201893

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 201893

Rationale

The Bromodomain (BRD) and Extra-Terminal (BET) family is comprised of four different proteins that bind via their bromodomains to acetylated histone tails in order to regulate transcription, cell growth, and survival. In preclinical models, small molecules that inhibit the binding of BET proteins to histones have been associated with potential therapeutic benefit for multiple human malignancies. The study drug, GSK2820151, is a BET inhibitor arising from a distinct structural class to that previously progressed to clinical studies. GSK2820151 potently inhibits tumor growth *in vitro* and *in vivo* in animal models. This first time in human (FTIH), open-label, dose escalation study will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK2820151 in subjects with advanced or recurrent solid tumors.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK2820151 in subjects 18 years or older with advanced or recurrent solid tumors.	• Adverse events (AEs), serious adverse events (SAEs), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, electrocardiogram (ECG), cardiotoxicity, gastrointestinal, etc.)
Secondary	
• To determine a recommended Phase 2 dose (RP2D) of GSK2820151 in subjects 18 years or older.	• Safety profile (AEs, SAEs, dose-limiting toxicities [DLTs]), clinical response, and PD data
• To characterize the pharmacokinetics (PK) of GSK2820151 in subjects 18 years or older.	• PK parameter values for GSK2820151 following single and repeat-dose oral administration in subjects 18 years or older.
• To evaluate the effect of treatment with GSK2820151 on tumor growth and subject survival.	• Objective response rate (ORR) by various imaging modalities and progression free survival (PFS).
• To evaluate cardiac safety, including the potential for corrected QT interval (QTc) prolongation, of GSK2820151 and to assess PK/QTc relationship.	• Changes in cardiac safety including QTc following single and repeat-dose oral administration of GSK2820151.
Exploratory	
• To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK2820151 and safety and efficacy parameters.	• Dose-related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in peripheral blood samples.
• To evaluate systemic and *ex vivo* on-target	• Changes from baseline and dose/response

Objectives	Endpoints
BET inhibitory effects	relationship in *ex vivo* lipopolysaccharide (LPS)-induced cytokines, including Interleukin 6 (IL-6), in whole blood, and systemic cytokines, including IL-6.
• To identify potential indicators of sensitivity or response to GSK2820151.	• Transcriptomic studies of blood; correlation of baseline genetic and genomic profiles with response.

Overall Design

This study is a single-arm, open-label, dose-escalation study to determine the MTD (and a RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK2820151. Eligible subjects with advanced or recurrent solid tumors will be enrolled in the dosing cohorts until an MTD is established.

Treatment Arms and Duration

This is a single-arm study in which all subjects will receive the investigational agent. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. The duration of study will depend on recruitment rates and the timing of subjects' duration on study (withdrawal rates due to toxicity or progression), with an approximate duration of 3 years.

Type and Number of Subjects

Approximately 30 to 50 subjects with will be enrolled in the study. The study population will be adults, with advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable, who either:

- refuse standard curative or palliative therapy,
- are not candidates for standard curative or palliative therapy,
- have a disease for which no non-investigational therapy exists, OR
- have progressed on prior therapy (radiographic documentation of progression is adequate for study participation).

The total number of subjects required will depend upon the number of escalation steps required to reach a MTD.

Analysis

After each dosing cohort, a Continual Reassessment Method (N-CRM) analysis will be used to recommend the next dose level based on observed dose-limiting toxicities (DLTs). Dose escalation decisions will be based on the totality of clinical safety assessment based on a combination of reported safety events, N-CRM recommendation, as well as pharmacokinetic and pharmacodynamic data.

All data will be pooled and descriptive analyses summarized and listed by cohort at study conclusion. No formal statistical hypotheses will be tested. Analyses will be descriptive and exploratory.

Measurements

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There will be extensive PK sampling during this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Blood samples will be collected for analysis of protein biomarkers (cytokines and acute phase proteins) and messenger ribonucleic acid (mRNA). LPS induction of cytokines in whole blood will be assessed.
- **EFFICACY MEASUREMENTS**: ORR and PFS.
- **SAFETY MEASUREMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events will be performed. Stringent cardiac safety monitoring will be required, consisting of:
  - ≥ 48 hours of telemetry following the first dose (necessitating overnight stays in a research facility)
  - 24 hours of ambulatory cardiac (Holter) monitoring in Week 1, Week 2, Week 3, and Week 9
  - Triplicate 12-lead ECGs prior to dosing on selected days and prior to drawing PK samples on serial PK sampling days.

  Extensive laboratory testing includes standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels. Troponin, C-peptide, 1,5-anhydroglucitol, glycosylated hemoglobin (hemoglobin A1c), and thyroid monitoring will also be performed.

2. INTRODUCTION

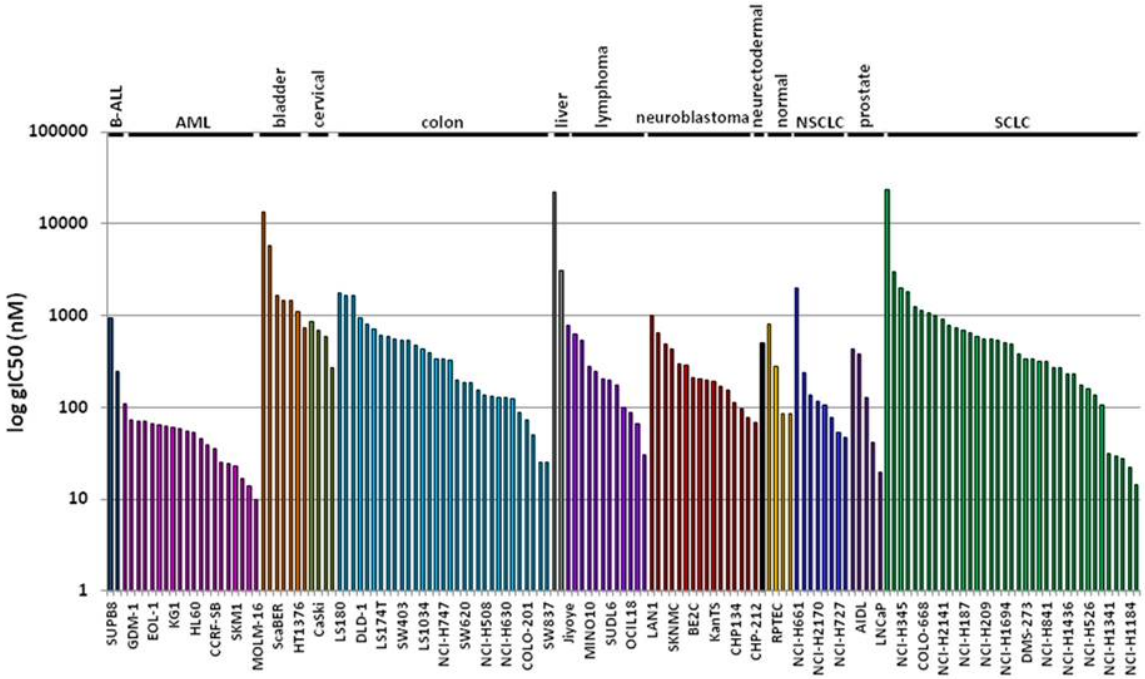
GSK2820151 is a novel, orally available inhibitor of the Bromodomain (BRD) and Extra-Terminal (BET) family of bromodomain-containing transcriptional regulators that is being developed for treatment of multiple solid malignancies.

2.1. Study Rationale

The aim of this study is to establish a maximum tolerated dose for the BET inhibitor GSK2820151 in subjects with refractory, advanced solid malignancies where prognosis is particularly poor with limited effective treatment options. Preclinical studies have shown that small molecule-based inhibition of BET protein binding to chromatin with GSK2820151 inhibits proliferation of multiple solid tumor-derived cancer cell lines and results in significant anti-tumor activity in animal models of advanced disease [Chaidos, 2014; Wyce, 2013].

Consistent with the published literature, GSK2820151 inhibits proliferation and induces a cytotoxic response in cell lines across a wide range of solid tumor types (Figure 1). GSK2820151 inhibits growth in a broad spectrum of human solid cancer and hematological (heme) cell lines. These include Nuclear protein in testes (NUT) midline carcinoma (NMC), non-small cell lung cancer (NSCLC), neuroblastoma, cervical cancer, prostate cancer, small cell lung cancer (SCLC), colorectal cancer (CRC), acute myeloid leukemia (AML), multiple myeloma (MM), and lymphoma. By way of example in the largest panel of cell lines tested (n=149), eighty seven percent are highly sensitive to GSK2820151, exhibiting growth half maximal inhibitory concentration (IC_{50}) (gIC_{50}) values below 1.0 μM (Figure 1)

Figure 1 Effect of GSK2820151 on the growth of human tumor-derived cell lines



Bromodomains (BRDs) are found in a variety of proteins that recognize and bind to acetylated histone tails [Dhalluin, 1999]. This binding affects chromatin structure and facilitates the localization of transcriptional complexes to specific genes, thereby regulating gene transcription and messenger ribonucleic acid (mRNA) elongation [Dey, 2003; Jang, 2005]. The BRD extra-terminal (BET) family of BRD proteins includes the BRD2, BRD3, BRD4, and BRDT proteins.

BET proteins have been shown to be involved in the regulation of transcription, cell growth, and survival. In addition, BRD4 has been shown to be directly involved in regulation of the cell cycle, as it remains associated with chromosomes through mitosis, specifically at the transcription start site (TSS) of genes expressed at the M/G1 phase of the cycle [Dey, 2009]. BRD4 is also a critical mediator of transcriptional elongation, functioning to recruit the positive transcription elongation factor complex (P-TEFb) [Itzen, 2014; Patel, 2013]. BRD4 inhibition, through blocking P-TEFb recruitment to chromosomes, results in decreased expression of growth-promoting genes [Hargreaves, 2009].

The investigational agent GSK2820151 is a potent inhibitor of the BET family of proteins. The crystal structure of GSK2820151 in complex with the bromodomain 1 of BRD4 reveals the compound to bind as a histone mimetic. This binding mode has been shown previously for other compounds to inhibit the assembly of the transcriptional complex and the subsequent gene expression response [Nicodeme, 2010].

The role of BET proteins in malignancy is best demonstrated in Nuclear Protein in Testes (NUT) midline carcinoma (NMC), a rare, aggressive, and invariably lethal tumor with a median overall survival of 6.7 months [Bauer, 2012]. NMC is triggered by a translocation between the NUT gene and one of the BRD genes (typically BRD3 or BRD4) [French, 2008]; the resulting fusion oncoprotein is retained in the cell nucleus via interactions with chromatin [Yan, 2011]. Treatment of patient-derived NMC lines with small molecule BET inhibitors leads to rapid growth inhibition and differentiation of cells to a non malignant phenotype. This has led to the further clinical investigation of compounds for this patient population.

While NMC is the prototypic BET-driven malignancy, other tumor types have been found to require functional BET for growth and progression [Fiskus, 2014; Trabucco, 2014; Asangani, 2014]. Studies in leukemia and multiple myeloma (MM) cell lines have shown that small molecule inhibition of BET protein binding to chromatin can directly block expression of the gene *myc* and its downstream transcriptional functions, resulting in significant anti-tumor effects [Delmore, 2011; Mertz, 2011]. GSK2820151 has been studied extensively in cell culture and has been demonstrated to inhibit the growth of multiple solid tumor cell lines apart from NMC, including those derived from cancer of the bladder, breast, cervix, colon/rectum, prostate, and lung (see Figure 1 as well as investigator's brochure [IB], Section 5.2.1.1 [GlaxoSmithKline Document Number 2014N208278_00]). GSK2820151 has also demonstrated efficacy after oral administration in mouse xenograft models of SCLC and NMC (see IB, Section 5.2.1.2 [GlaxoSmithKline Document Number 2014N208278_00]). Based on these observations, administration of GSK2820151 to humans is expected to have potential therapeutic applications in a broad array of solid malignancies.

Importantly, while the biochemical and phenotypic properties of GSK2820151 are comparable to those reported for BET inhibitors under clinical evaluation from the

benzodiazepine class, this agent is the first of its structural class to enter clinical trials. As such differential human pharmacokinetics, pharmacodynamics, or overall safety profile for GSK2820151 may provide beneficial improvements in therapeutic index for patients. It is on this basis that clinical trials with GSK2820151 are being proposed.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the safety, tolerability and maximum tolerated dose (MTD) in subjects 18 years or older with advanced or recurrent solid tumors.	• Adverse events (AEs), serious adverse events (SAEs), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, electrocardiogram (ECG), cardiotoxicity, gastrointestinal, etc.)
Secondary	
• To determine a recommended Phase 2 dose (RP2D) of GSK2820151 in subjects 18 years or older.	• Safety profile (AEs, SAEs, dose-limiting toxicities [DLTs]), clinical response, and PD data
• To characterize the pharmacokinetics (PK) of GSK2820151 in subjects 18 years or older.	• PK parameter values for GSK2820151 following single and repeat-dose oral administration in subjects 18 years or older.
• To evaluate the effect of treatment with GSK2820151 on tumor growth and subject survival.	• Objective response rate (ORR) by various imaging modalities and progression free survival (PFS).
• To evaluate cardiac safety, including the potential for corrected QT interval (QTc) prolongation, of GSK2820151 and to assess PK/QTc relationship.	• Changes in cardiac safety including QTc following single and repeat-dose oral administration of GSK2820151.
Exploratory	
• To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK2820151 and safety and efficacy parameters.	• Dose-related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in peripheral blood samples.
• To evaluate systemic and *ex vivo* on-target BET inhibitory effects	• Changes from baseline and dose/response relationship in *ex vivo* lipopolysaccharide (LPS)-induced cytokines, including interleukin 6 (IL-6), in whole blood, and systemic cytokines, including IL-6.
• To identify potential indicators of sensitivity or response to GSK2820151.	• Transcriptomic studies of blood; correlation of baseline genetic and genomic profiles with response.

4. STUDY DESIGN

4.1. Overall Design

This study is a single-agent, open-label, dose-escalation study to determine the MTD (and RP2D), based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK2820151. Eligible subjects with advanced or recurrent solid tumors will be enrolled in the dosing cohorts until MTD is established. All subjects will receive study drug. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent (for specific stopping criteria, see Section 5.4). The duration of study will depend on recruitment rates and the timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

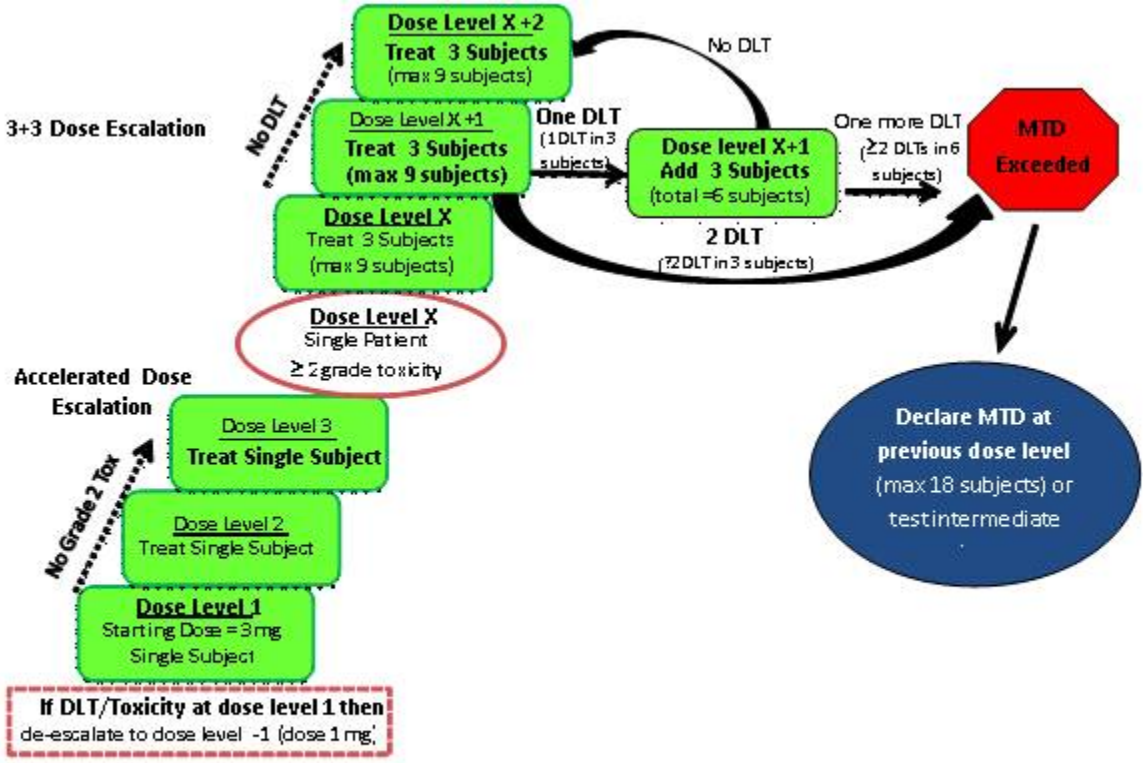
4.2. Dose Escalation and Duration of Study

This study will utilize an accelerated dose escalation phase in order to minimize sub-optimal drug exposures, followed by a conventional 3+3 dose escalation phase to achieve MTD. Initially, one subject per dose cohort will be recruited *(accelerated dose escalation phase)* until the first instance of a ≥ Grade 2 drug related non-hematological toxicity or dose-limiting toxicity (DLT, see Section 4.2.4). Further cohorts will be recruited in blocks of three subjects *(3+3 dose escalation phase).* Additional subjects may be enrolled at previously cleared dose levels in order to obtain further data for PK and/or PD analysis. *Once MTD is determined, additional subjects (18 subjects total at MTD) may be enrolled to collect additional safety data (*Figure 2*). The total duration of study for each subject will be dependent upon the safety, tolerability and efficacy of GSK2820151.*

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on PK data, the safety profile of the current and prior cohorts, as well as the predicted dose-limiting toxicity (DLT) rates on all potential doses from the Neuenschwander Continual Reassessment Method (N-CRM) analysis [Neuenschwander, 2008]. N-CRM design is a type of Bayesian adaptive dose-escalation scheme (see Section 11.2). The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The DLT information of all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

The RP2D will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile, and available PD data generated from all subjects (Table 2). If necessary alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

Figure 2 Dose Escalation Scheme



(Dose increase at any dose escalation will be ≤2 fold.)

4.2.1. Planned Dose Levels

Projected dose levels are 3 mg, 6 mg, 12 mg, 20 mg, 40 mg, 60 mg, 100 mg, 150 mg, 200 mg, and 300 mg. Additional doses and schedules may be explored based on emerging safety, PK, and PD data.

4.2.2. Accelerated Dose Escalation

One subject per dose level in the accelerated dose escalation phase will be treated to minimize suboptimal drug exposures, starting with Dose Level 1 and will continue until one subject experiences ≥ Grade 2 drug related toxicity (based on National Cancer Institute- Common Terminology Criteria for Adverse Events, Version 4 (NCI-CTCAE v4.03 [NCI-CTCAE, 2010]) or dose-limiting toxicity (DLT, see Section 4.2.4). The accelerated dose titration scheme is described in Table 1. A single dose (Day 1) will be given to subjects in each cohort with the collection of blood samples for PK analysis at timed intervals. Once the final PK sample for Day 1 is obtained, subjects may begin repeat dosing on Day 3. The dose for Dose Level 2 and subsequent cohorts will be based on the pharmacokinetics (PK) and safety analysis of the previous cohort. Inter-subject variability in exposure and toxicity will also be considered when deciding on actual doses administered during dose-escalation. Dose escalation will occur according to the procedures outlined in Table 1.

A sufficient number of subjects will be enrolled in each cohort to ensure that data from at least one subject that has completed a full treatment cycle (4 weeks) of dosing is available prior to defining a new dose and starting the next cohort. The dose-escalation decision and rationale for the subsequent cohort(s) will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

At the first occurrence of a DLT (refer to Section 4.2.4) or any Grade 2 toxicity based on NCI-CTCAE v4.03 (with the exception of Grade 2 alopecia, nausea, vomiting, diarrhea, hemoglobin, lymphopenia, taste changes or alkaline phosphatase in the presence of bony metastases) during the first 4 weeks, the Accelerated Dose Titration phase will be terminated and the ongoing cohort will be expanded up to 6 subjects to commence the 3 + 3 Dose-Escalation phase of the study.

Table 1 Accelerated Dose Titration Procedures

Dose Level	Toxicity	Dose Escalation
Accelerated Dose Titration Phase		
Dose Level -1		Lower doses may be explored if DLTs or significant toxicities are observed at Dose Level 1.
Dose Level 1		Starting Dose: 3 mg daily
Subsequent Dose Levels	No subjects with either a ≥ Grade 2 toxicity or a DLT in first 4 weeks of treatment	Escalate to next dose level with an increase of ≤ 100%[a]
End of Accelerated Dose Titration Phase	One or more subjects with a ≥ Grade 2 toxicity or a DLT in first 4 weeks of treatment	Begin 3+3 dose-escalation phase

a. Dose levels in Section 4.2.1 are suggestions; the final determination of the next dose level will be made at the dose escalation meeting in concert with the Investigators, GSK Medical monitor, and representatives from Safety, Statistics, and Clinical Pharmacology. The final dose escalation decision will depend on all factors, as described in Section 11.2.1.

4.2.3. 3 + 3 Dose Escalation

If the accelerated dose titration ends due to ≥ grade 2 toxicity then two additional subjects will be enrolled to same dose level where as, if termination of accelerated dose titration is due to DLT, then up to 5 additional subjects will be enrolled at the same dose level to continue the treatment following the 3 + 3 Dose Escalation guidelines. Subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the MTD in multiple subjects. Dose escalation decisions will be made as outlined in Table 2 Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. Intra-subject dose escalation may be considered as described in Section 4.2.7. Subjects should not be enrolled at a higher dose level until at least 3 subjects in the previous dose cohort complete 4 weeks of treatment.

Dose-limiting toxicity (DLT) is based on any observed toxicity in the first 4 weeks. If 1 of 3 subjects experiences a DLT at a particular dose level, 3 additional subjects will be enrolled at that dose level. If 2 or more subjects experience a DLT at a particular dose

level, a lower (or intermediate) dose level may be explored to better define the maximum tolerated dose (MTD).

If 2 or more DLTs in 6 subjects are observed at any dose level, the MTD will have been exceeded (Table 2).

Table 2 3 + 3 Dose Escalation Design

Number of Subjects with DLT in a Cohort	Action
0 out of 3 subjects	Escalate to next dose level with an increase of ≤ 100%[a] • If two or more subjects have the same ≥ Grade 2 drug-related adverse event, consider a <2-fold increase[a] taking into consideration the safety profile and dose-exposure relationship
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to the next dose level with an increase of ≤50%[a]
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to a total of 12 subjects
1 or more out of 6 subjects at the highest dose level below the MTD	The dose is considered the recommended Phase 2 dose (RP2D). At least 6 subjects must be evaluated at the RP2D dose.

a. Dose levels in Section 4.2.1 are suggestions; the final determination of the next dose level will be made at the dose escalation meeting in concert with the Investigators, GSK Medical monitor, and representatives from Safety, Statistics, and Clinical Pharmacology. The final dose escalation decision will depend on all factors, as described in Section 11.2.1.

The RP2D will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile, and available PD data generated from all subjects. If necessary alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

4.2.4. Dose-Limiting Toxicity

An event is considered to be a dose-limiting toxicity (DLT) if the event is attributed (definitely, probably or possibly) to the study treatment during the first 4 weeks of treatment and meets the criteria described in Table 3, as graded when applicable by the NCI-CTCAE v4.03.

Subjects who are unable to receive at least 75% of the scheduled doses during the 4-week DLT evaluation period will be replaced in the cohort unless the reason for the delay or discontinuation was due to a DLT.

Table 3 Dose –Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 for ≥5 days) • Febrile neutropenia (as defined by NCI-CTCAE v4.03 [concurrent Grade 4 neutropenia and fever >38.3°C]) • Grade 4 anemia of any duration • Grade 3 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia (platelets <25,000/mm^3)
Non-hematologic	• Alanine aminotransferase (ALT) >3x upper limit of normal (ULN) + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin < 2xULN but with hepatitis symptoms or rash (See Section 5.4.1 for Liver Stopping Criteria) • Grade 3 nausea, vomiting or diarrhea that does not improve within 24h despite appropriate supportive treatment(s) • Grade 4 nausea, vomiting, or diarrhea • Grade 3 hypertensiona[a] (uncontrolled despite addition of up to 2 antihypertensive medications) • Grade 4 hypertension • Grade 3 or greater clinically significant non-hematologic toxicity (including QTc corrected by Fridericia's formula [QTcF]) per NCI-CTCAE, v4.03 except toxicities listed in Section 4.2.5 • Grade 2 troponin b elevation (central laboratory >ULN), measured on two separate occasions within 48 hours in order to confirm elevation and with other clinical signs, symptoms, laboratory tests consistent with cardiac toxicity[b].
Other	• Any toxicity resulting in a dose delay of >14 days of the intended next dose • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

Toxicity Grading based on NCI-CTCAE v4.03

a. Grade 3 hypertension adequately controlled by antihypertensive medication(s) is not considered to be a DLT.

b. In the event a troponin (central laboratory assessment) is not performed or a laboratory error occurs, considerations for a DLT criterion will involve review of two separate local troponin (I or T) assays done within 48 hours at a local investigator site. Troponin I or T elevations greater than the upper limit of normal, and > 10% coefficient of variance (CV%) for that assay will be considered as a grade 2 elevation.

4.2.5. Non-Limiting Toxicities

The following toxicities have been deemed to be non-serious for the purposes of this study. These toxicities will not be taken into account for dose escalation decisions unless, in the opinion of the investigator and the GSK Medical Monitor, they represent a dose-limiting toxicity. For all other toxicities and their management, see Section 14.7.

- Grade 3 or less:
    - Fatigue
    - Rash
    - Mucositis
    - Asthenia
    - Alopecia
- Electrolyte imbalance or other laboratory abnormalities controlled within 24h

4.2.6. Alteration of Schedule

Alterations may be made to the schedule of administration and/or PK/PD sampling schedule based on the results of emerging PK and safety data.

Schedules that incorporate a recovery period may be explored (e.g., 2 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using 3 + 3 dose escalation.

Schedules that use a shorter recovery period, e.g., twice daily (BID) dosing, may also be explored. This approach will be considered if the safety, PK, and emerging PD data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule. If a shorter recovery period is used, the initial dose level will be ≤50% of the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using the 3 + 3 dose escalation. Alternative schedules with intense supportive care may also be explored.

The dosing schedule may also be adjusted to expand a prior dose cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

4.2.7. Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced any Grade 2 or higher drug related toxicity prior to dose escalation in the accelerated dose escalation phase or a DLT in the 3+3 dose escalation phase and contingent upon the following:

Additional subject(s) have been enrolled at a higher dose in the dose escalation phase and at least one subject has completed 4 weeks of dosing on that regimen without a DLT; and after review of all safety data and approval by a GSK Medical Monitor, a subject on a lower dose level may be increased up to the highest dose level tested. In this case the subject may begin dosing at the higher dose level as it will have already been demonstrated to be tolerable.

Subjects approved for intra-subject dose escalation will require additional limited PK sampling at the higher dose, as determined by GSK Clinical Pharmacology. Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

4.3. Type and Number of Subjects

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) of GSK2820151 for further study. It is estimated 30 to 50 evaluable subjects will be enrolled.

Approximately 30 to 50 subjects with refractory, histologically or cytologically confirmed, advanced (metastatic or unresectable) solid malignancies will be enrolled in the study. The study population will be adults, with advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable, who either:

- refuse or are not candidates for standard curative or palliative therapy
- have a disease for which no non-investigational therapy exists
- have progressed on prior therapy (radiographic documentation of progression is adequate for study participation).

If a subject discontinues the study before completing Week 4 due to reasons other than toxicity, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator to ensure an adequate population for DLT and MTD evaluations.

4.4. Design Justification

Given the high unmet medical need of relapsed/refractory, advanced solid tumors, a conventional Phase I study (201893) is proposed. The study comprises an accelerated dose titration to determine a MTD. While preliminary efficacy data will be collected as part of the course of the study, it will not be a primary endpoint. Overall, the aim of the study is to identify a RP2D for future evaluation of GSK2820151.

While dose escalation and subject enrollment will utilize a conventional 3+3 approach, determination of the particular dose to be tested in each cohort will utilize all available information, including input from the N-CRM model. The updated model from the N-CRM analysis after each subject is evaluated will give more information about the expected DLT rate at each dose level and assist in the dose-escalation decision making process.

4.5. Dose Justification

4.5.1. Human Pharmacokinetic Extrapolation

Human pharmacokinetics was predicted based on three species (mouse, rat and dog) using different allometric extrapolation. Whole blood human clearance predicted from mean of allometry was 6.5 ml/min/kg (~30% hepatic blood flow). Volume of distribution at steady state was predicted to be 2.8 L/kg with a moderate half life of ~5hr. Bioavailability is predicted to be ~69%.

4.5.2. Starting Dose

The 28 day toxicology studies were conducted using the freebase of GSK2820151 whereas the mesylate salt of GSK2820151 will be used on this clinical study. Comparison of systemic exposure between the freebase and mesylate versions of GSK2820151 at the same dose level (corrected for form) showed that systemic exposure was comparable in the rat, but the mesylate salt resulted in 2-4.6 fold higher exposure in the dog. Taking into account the difference in systemic exposure for the dog (and using the more conservative approach of 4.6 fold difference), the dose level required to achieve equivalent systemic exposure has been adjusted (i.e. highest non-severely toxic dose (HNSTD) freebase of 5 mg/kg is equivalent to HNSTD mesylate of 1.09 mg/kg.).

Three approaches have been considered to establish the starting dose for GSK2820151.

- One tenth of the rat severely toxic dose in 10% of the animals (STD10)

  For GSK2820151, the STD10 was defined as 3 mg/kg in the rat following International Conference on Harmonization (ICH) S9 guidelines. 1/10 rat STD10 is 1.8 mg/m^2; this dose is not severely toxic to dogs and translates to a starting dose in man of 3 mg, assuming a 70 kg adult and adult surface area of 1.7 m^2.

- One sixth of the dog HNSTD

  For GSK2820151, the dog HNSTD is defined as 1.09 mg/kg. 1/6 dog HNSTD is 3.63 mg/m^2 which translates to a starting dose in man of 6 mg, assuming a 70 kg adult and adult surface area of 1.7 m^2.

- The dose predicted to deliver a minimum anticipated biological effect t level minimum anticipated biological effect level, (MABEL) dose.

The potential therapeutic effect of GSK2820151 was evaluated at single oral daily doses of 10 mg/kg (30 mg/m^2) and 30 mg/kg (90 mg/m^2) in OPM-2 transgenic non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mouse xenograft model of multiple myeloma; 25 mg/kg (75 mg/m^2) daily and 50 mg/kg (150 mg/m^2) every other day in NCI-H526 SCLC xenograft model and 30 mg/kg (90 mg/m^2) daily in NMC xenograft model. GSK2820151 was efficacious at 30 mg/kg in both studies and showed partial efficacy at 10 mg/kg dose in OPM-2 xenograft model. 25 mg/kg dose showed ~24% reduction in tumor growth while 50 mg/kg showed ~54% reduction in tumor volume. The mouse MABEL dose of 10 mg/kg (30 mg/m^2) would translate to a dose in

human of 125 mg using human equivalent dose calculation. Taking a conservative approach, the starting dose will be 3 mg.

The predicted human exposure at 3 mg is area under the curve from zero to 24 hours (AUC_{0-24}) = 78.8 ng/h/mL and is approximately 6-fold lower than the exposure at the dog NOAEL / HNSTD and approximately 9- and 47-fold lower than the rat no observed adverse effect level (NOAEL) and STD10 exposures, respectively.

4.6. Benefit: Risk Assessment

Summaries of findings from the non-clinical studies conducted with GSK2820151 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2014N208278_00]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiovascular Effects	**QT Prolongation** QT prolongation was observed in dogs after single dosing (≥ 10 mg/kg; up to 34 milliseconds [msec] and up to 48hr post dosing) and after repeat dosing (≥ 30 mg/kg/day from Day 3; up to 21 msec). A direct effect on human *ether-à-go-go*-related gene [hERG] binding is unlikely.; Mechanism and risk for Torsades de Pointes is unclear. Increased number of non-fatal arrhythmias were observed in 1 of 4 dogs which had highest drug exposure after a single dose of 100mg/kg (10x the dog 28 day maximum tolerated dose, or MTD). **Blood Pressure (BP)** Increases in blood pressure (mean, systolic & diastolic; systolic affected more than diastolic) were observed in dogs after single dosing ≥ 10 mg/kg(mean up to 38 millimeters mercury [mmHg] and up to 42 hours post dosing). **Heart Rate**	Informed consent form (ICF) includes the risk of (fatal) arrhythmias and the risk of myocardial infarction Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 7.1.2). Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK], creatine kinase-MB isoenzyme [CK-MB], and troponins [local laboratory monitoring for troponin I or T based on availability and troponin T at central laboratory]), cardiac monitoring (ECGs, Holter monitoring and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management of cardiac events (refer to Section 14.7.1). All subjects will receive their first dose of study medication (Week 1 Day 1) in the hospital with telemetry monitoring for the first 48 hours of dosing. Throughout the protocol, the role of intensive cardiac monitoring will be re-evaluated in an ongoing fashion with the aim of re-evaluating cardiac risk mitigation strategy while

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Increased heart rate was observed after single dosing (100 mg/kg; up to 24 beats per minute [BPM] between 9 and 19 hours post dosing) and in one dog after repeat dosing (100 mg/kg; up to 64 BPM post dosing). **Cardiac Biomarkers** Reversible increases in serum cardiac troponin I (cTnI) levels were observed in male rats (up to 3.3X) at 10 mg/kg/day for 28 days. Increased NT pro-ANP (up to 2.1X) in female rats given ≥1 mg/kg/day for 28 days; no recovery after up to 5 weeks off dose period. No histologic lesions were observed in the heart on 28 day studies.	maintaining subject safety.
Gastrointestinal (GI) Effects	Gastrointestinal effects were the dose limiting toxicity (DLT) observed following repeat dosing in rats (≥3 mg/kg/day) and dogs (≥10 mg/kg/day) Clinical presentation included altered feces, reduced food consumption and body weight reductions. These changes correlated with microscopic findings throughout the GI tract of rats given ≥6 mg/kg/day and dogs at 20 mg/kg/day. Microscopic findings in rats and dogs included erosion/ulceration, mucosal epithelium degeneration/regeneration and	ICF includes the risk of gastrointestinal effects. Protocol includes medical history, physical examination (including weight) and clinical laboratory assessments to assess toxicity in the GI tract. Subjects with a history of gastrointestinal bleeding in the past 6 months (Section 5.2) or active bleeding will be excluded. Protocol also includes specific dose adjustment/stopping safety criteria for diarrhea and mucositis (refer to Section 14.7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	inflammatory cell infiltration. Microscopic findings in dogs only included minimal to mild hemorrhages, villous atrophy and mild cecal lamina propria fibrosis . Signs of recovery were observed immediately after cessation of dosing; no abnormal microscopic findings were evident following a 3 to 5 week off dose period.	
Lymphoid/Hematologic Effects	Lymphoid / hematologic toxicity was observed in rats given ≥3 mg/kg/day and in dogs given ≥5 mg/kg/day . The effects manifested as hypocellularity in bone marrow, thymus and lymph nodes of rats and dogs and reduced cellularity of the spleen in rats. This was accompanied peripherally by evidence of increased red cell turnover and/or mild haemolysis, reductions in red blood cells, platelets, basophils, eosinophils, lymphocytes, and increases in neutrophils (in response to GI toxicity). Effects on reticulocyte counts were variable. Regenerative response in blood cell parameters and microscopic observation of extramedullary haematopoiesis and increased cellularity in the lymph nodes and spleen was evident after up to five weeks off dose. Increased activated partial thromboplastin time (APTT) was observed in male rats given ≥1 mg/kg/day and in dogs given	ICF includes the risk of lymphoid / hematologic toxicity. Protocol includes laboratory assessments (complete blood count [CBC] and coagulation factors [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], exclusion criteria if there is evidence of clinically significant bleeding episodes, monitoring for bruising/infection and dose stopping/modifications criteria (refer to Section 14.7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	20 mg/kg/day . A mild decrease in APTT was observed in female rats given 3 mg/kg/day. Increases in fibrinogen was observed in dogs given 20 mg/kg/day. All of these effects were reversible.	
Reproductive Effects	Animal reproductive studies have not been conducted with GSK2820151. No ovarian changes were observed in toxicology studies of up to 4 weeks duration; however, an assessment of estrous cycling was not conducted. BRD2, BRD3, BRD4 and BRDT have crucial roles in reproduction and development [Paillisson, 2007; Trousdale, 2004] and would be expected to adversely affect embryofetal development. A compound with a similar pharmacology profile has shown detrimental effects on rat female fertility and embryo-fetal development (EFD) at clinically relevant exposures. This information indicates that GSK2820151 will likely have similar effects on female fertility and EFD. Testicular degeneration was observed in rats given ≥ 10 mg/kg/day and dogs given ≥5 mg/kg/day. Disorganized spermatogenesis was also observed in dogs. Secondary changes	ICF includes the risk of damage to reproductive organs such as testes or ovaries including potential risk to embryofetal development. Protocol (refer to Section 7.3) includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and complete) for male subjects. Due to the effects of GSK2820151 on the male reproductive system were observed in pre-clinical settings and potential for GSK2820151 to be present in semen, men should adhere to the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	in epididymides were also evident (hypospermia, degenerate germ cells and/or epithelial vacuolation in both species, and atrophy in dogs only). There was no evidence of reversibility of these findings within a three-week off dose period, but due to the length of the spermatogenic cycle (approximately two months), recovery may occur following a longer off dose period. Reduced prostate weight was observed in rats and dogs. Additionally, in rats, decreased secretory content in prostate (dosing at ≥3 mg/kg/day) and in seminal vessels (dosing at 10 mg/kg/day) were observed. These effects were reversible.	contraceptive guidance detailed in the protocol (refer to Section 7.3.2).
Hepatobiliary Effects	Reversible minimal vacuolization of the gallbladder and biliary epithelium were observed in dogs given ≥ 10 mg/kg/day. Decreased inflammatory cell infiltrate was observed in rats given ≥ 3 mg/kg/day and was still evident in some animals after an off dose period of up to 5 weeks. This is considered indicative of the anti-inflammatory pharmacology of BET bromodomain and extra-terminal inhibitors..	ICF includes the risk of hepatobiliary effects. Protocol includes hepatic eligibility criteria, laboratory assessments during the study, and dose stopping/modifications criteria for the management of hepatic events (refer to Section 14.3 & Section 14.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Lung Effects	Minimal to mild prominent (foamy) alveolar macrophages were observed in rats administered ≥ 1 mg/kg/day. These effects were reversible. The clinical consequences of this finding are unknown.	ICF includes the risk of lung effects. Protocol includes pulmonary function assessments at screening and as clinically appropriate afterwards (subjects with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage, chest radiation) chest x-ray at baseline and dose stopping/modifications criteria for pneumonitis (refer to Section 14.7.1).
Effects on Teeth	Minimal to mild changes related to dentin formation in continuously growing incisors were observed in rats given ≥ 3 mg/kg/day. A marginally increased incidence and/or severity occurred after off dose period. No changes were observed in molar teeth of dogs.	Due to the differences between rodents and human, it is unlikely that these effects of teeth will affect human adults.

4.6.2. Benefit Assessment

Study 201893 is an open-label, dose escalation study and the first study of this agent to be conducted in subjects with relapsed and/or refractory advanced solid malignancies for which no standard therapies are available. GSK2820151 has promising preclinical activity in cell lines; however it is unknown whether GSK2820151 will have clinical efficacy in subjects with solid tumors. As such, any potential beneficial effect for an individual subject attributable to GSK2820151 is unknown. Data obtained in Study 201893 may assist in progressing the knowledge base on advanced malignancies and their treatment, or help identify individuals more likely to benefit or have side effects from GSK2820151.

4.6.3. Overall Benefit:Risk Conclusion

Current data from preclinical development indicate GSK2820151 inhibits the BET family of BRD proteins, and that this inhibition may have clinical utility in the treatment of various tumors. Taking into account the measures taken to minimize risk to subjects participating in the Phase I clinical trials, the potential risks identified in association with GSK2820151 are justified by the anticipated benefits that may be afforded to subjects with relapsed/refractory advanced solid malignancies with otherwise limited therapeutic options.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the GSK2820151 Investigator Brochure [GlaxoSmithKline Document Number 2014N208278_00]. *Approximately 30-50 subjects with relapsed or advanced solid malignancies will be enrolled. All subjects must have failed* refused or otherwise be ineligible for standard therapy, or have a tumor for which there is no standard therapy, *prior to consideration for study. The total number of subjects required will depend upon the number of escalation steps required to reach a MTD.*

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and enrolled

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Written informed consent provided
2. Males and females 18 years old and greater

3. Diagnosis of advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable. At time of enrollment, subjects either:
   - refuse or are not candidates for standard curative or palliative therapy
   - have a disease for which no non-investigational therapy exists
   - have progressed on prior therapy (radiographic documentation of progression is adequate for study participation).
4. Subjects with solid tumors, with the exception of castration-resistant prostate cancer (CRPC), must demonstrate measurable disease, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
5. All prior treatment- related toxicities must be NCI-CTCAE v4.03 ≤ Grade 1 (except alopecia [permissible at any Grade] and peripheral neuropathy [which must be ≤ Grade 2]) at the time of treatment allocation.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 1 (See Appendix 2 for definitions).
7. Adequate Baseline organ function as defined in Table 4.

Table 4 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 9 g/dL (subjects that required transfusion or growth factor need to demonstrate stable hemoglobin for 7 days of 9 g/dL)
Platelets	≥ 100 X 10^9/L
PT/INR and PTT	≤ 1.5 X upper limit of normal (ULN)
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 X ULN (isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome)
Alanine aminotransferase (ALT)	≤2.5 × ULN OR <5 x ULN is acceptable for subjects with documented liver metastases/tumor infiltration
Renal	
Creatinine OR Creatinine clearance [either directly measured or calculated by Cockcroft-Gault formula[b]]	≤1.5 X ULN ≥ 40 mL/min
Cardiac	
Ejection fraction	≥ 50% by echocardiogram
Troponin (T)	≤ ULN
Potassium	≥Lower limit of normal (LLN) and ≤ULN
Magnesium	≥LLN[a]

a. Magnesium supplementation is permitted, as required, to maintain a serum magnerium concentrations ≥ LNN
b. Cockcroft and Gault Method for Calculated Creatinine Clearance is provided in Appendix 9.

8. Able to swallow and retain orally administered medication.
9. A female subject is eligible to participate if she is of:
    - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation, hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, hysterectomy, or documented bilateral tubal oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) >40 U/ml and estradiol <40 pg/ml (<140 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
    - Child-bearing potential and agrees to use one of the contraception methods (described in Section 7.3) from the time of the screening pregnancy test until at least 7 months after the last dose of study medication.
    - Negative serum pregnancy test ≤ 7 days prior to first study drug dose, for women of childbearing potential.
    - Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 5 half-lives of GSK2820151 or at least 28 days (whichever is longer) following the last dose of study treatment.
10. Male subjects with female partners of child bearing potential must agree to use one of the methods of contraception specified (see Section 7.3.2). This method must be used from the time of the first dose of study medication until 16 weeks after the last dose of study medication. In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 16 weeks following the last dose of study medication.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Primary malignancy of the central nervous system or malignancies related to human immunodeficiency virus (HIV) or solid organ transplant.
2. Recent prior therapy, defined as follows:

a. Any investigational or Food and Drug Administration (FDA)-approved anti-cancer drug within 14 days or 5 half-lives, whichever is longer, prior to the first dose of GSK2820151. Note that an investigational drug is defined as a drug without an approved oncologic indication

b. Any radiotherapy, chemotherapy, targeted therapy or immunotherapy within 14 days or major surgery within 28 days or anti-neoplastic antibody or nitrosoureas/mitomycin C within 42 days prior to the first dose of GSK2820151.

c. Anti-androgen (e.g., bicalutamide) therapies for prostate cancer,, must be stopped 4 weeks prior to the first dose of GSK2820151. Second-line hormone therapies such as enzalutamide, abiraterone, or orteronel should be stopped 2 weeks prior to enrolment. Subjects with prostate cancer should remain on luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

d. In addition, any therapy-related toxicity must have resolved to Grade 1 or less, with the exception of alopecia (acceptable at any Grade) and peripheral neuropathy (which must be Grade 2 or less prior to enrollment).

3. Therapeutic anticoagulation (e.g., warfarin, heparin) must be discontinued 7 days prior to the first dose of GSK2820151 and coagulation parameters must be normalized prior to the first dose of GSK2820151. Low (prophylactic) dose low molecular weight heparin (LMWH) is permitted. In addition, INR must be monitored in accordance with local institutional practices.

4. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK2820151 (see Section 7.1.2 for the list of medications).

   NOTE: Aspirin up to 100mg PO daily is allowed. Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded except for cases where NSAIDs provide benefit over other analgesics (see Section 7.1.2 for details).

5. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

6. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

   NOTE: Subjects previously treated for these conditions that have had stable central nervous system (CNS) disease (verified with consecutive imaging studies) for >1months, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 1 month prior to study Day 1 are permitted. Stability of brain metastases must be confirmed with imaging. Subject treated with gamma knife therapy can be enrolled 2 weeks post-procedure as long as there are no post-

procedure complications/stable. In addition, subjects treated or currently taking enzyme-inducing anticonvulsant (EIAC) are allowed on study.

7. Cardiac abnormalities as evidenced by any of the following:
   - History of or current "untreated" clinically significant uncontrolled arrhythmias.
   - Clinically significant conduction abnormalities or arrhythmias
   - Presence of cardiac pacemaker
   - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
   - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing antithrombotic therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.
8. Following electrocardiogram (ECG) finding:
   - Baseline corrected QT (Fridericia's formula) interval (QTcF) ≥450 msec

   NOTE: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.

9. Any of the following liver findings:
   - ALT >2.5xULN
   - ALT > 5xULN with liver metastases/tumor infiltration
   - Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
   - Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).

   NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice or cirrhosis
10. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. History of known HIV infection.

    NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA polymerase chain reaction (PCR) is obtained.
11. Any serious known immediate or delayed hypersensitivity reaction(s) to GSK2820151 or idiosyncrasy to drugs chemically related to the investigational drug.

12. Hemoptysis > 1 teaspoon in 24 hours within the last 28 days.
13. Subjects with a history of known bleeding disorder(s) or history of clinical significant hemorrhage (e.g., gastrointestinal, neurologic) within the last 6 months.
14. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently dosed with study medication. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry, hematologic/non-hematologic toxicity, QTc prolongation, raised Troponin level as defined in Section 14.7.1 or left ventricular ejection fraction (LVEF)/valvular dysfunction as defined in Section 5.4.1 through Section 5.4.5. After disease progression, subjects may be allowed to continue treatment with study drug if the Investigator strongly believes, and the GSK Medical Monitor concurs, that the subject could continue to receive benefit (for example in cases of an isolated new lesion, with the majority of the disease still under control).

In addition study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in Time and Events Tables (see Section 8.1).

All subjects who permanently discontinue study treatment for any reason will be followed for survival and new anti-cancer therapy (including radiotherapy) every 6 months until death, termination of the study by the sponsor, or until the subject has been followed for 2 years. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression. If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).
The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

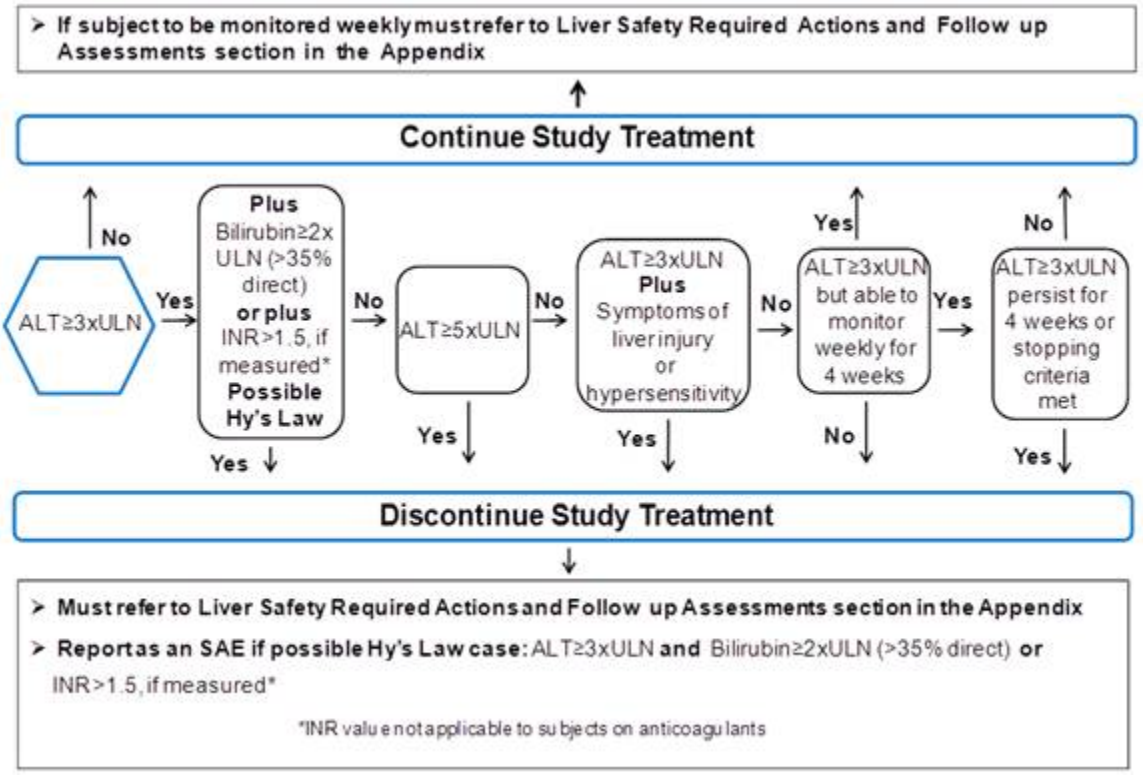
A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance):
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

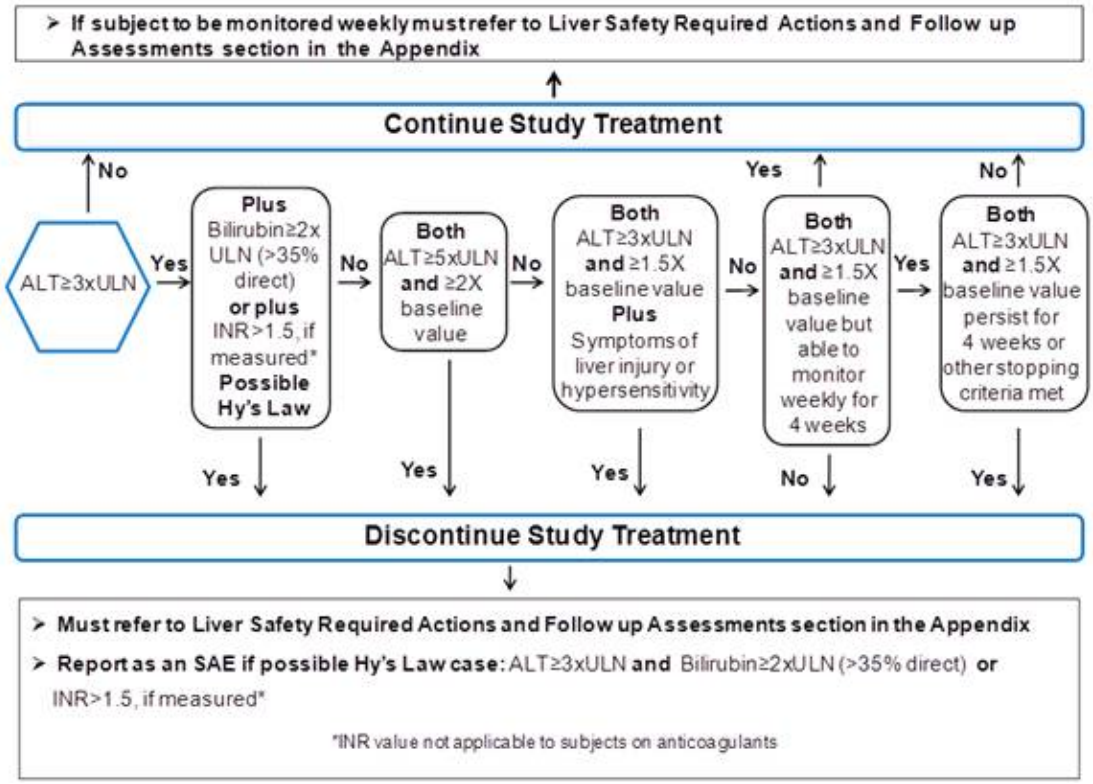
See Figure 3 and Figure 4 for liver stopping criteria for subjects without and with liver metastases, respectively.

Figure 3 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

Figure 4 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

5.4.1.1. Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted
- Ethics and/or institutional review board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 4 for full guidance.

5.4.2. QTc Stopping Criteria

If a subject meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QTcF interval ≥ 500 msec OR interval increase from baseline ≥ 60 msec: GSK2820151 will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the GSK Medical Monitor, as well as the GSK medical governance. In this situation, rechallenge may be permitted (see Appendix 7 for rechallenge guidelines).

NOTE: QT interval duration criteria should be based on the average QTc value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment discontinued.

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

- For eligibility and withdrawal, QTcF will be used for all subjects.
- For purposes of data analysis, QTcF will be used.

5.4.3. LVEF Stopping Criteria

Echocardiography must be performed at Screening, Week 5 Day 1, Week 9 Day 1, and every 8 week thereafter and at the post-treatment follow-up visit as outlined in the Time and Events Table (Section 8.1). Subjects who have an asymptomatic, absolute decrease of >10% in left ventricular ejection fraction (LVEF) compared with baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue GSK2820151 and have a repeat evaluation of LVEF within 1 week. Echocardiogram (ECHO) should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation with and approval from the GSK Medical Monitor, the subject may be restarted on GSK2820151 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK2820151 should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Subjects with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue treatment with GSK2820151. Ejection fraction should be monitored every

4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >institutional LLN and symptom resolution) within 4 weeks, treatment with GSK2820151 may be restarted at a reduced dose in consultation with the GSK Medical Monitor.

Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the Laboratory Manual.

5.4.4. Valvular Toxicity Stopping Criteria

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (ECHO) (Grade 2 mitral/tricuspid/aortic valvular toxicity per NCI-CTCAE v4.03) should temporarily discontinue GSK2820151 and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation with and approval from the GSK Medical Monitor, the subject may be restarted on GSK2820151 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK2820151. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK2820151. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart GSK2820151 at a reduced dose after consultation with and approval from the GSK Medical Monitor.

ECHO must be performed at baseline and at the final study visit. Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the Study Reference Manual (SRM).

5.4.5. Other Stopping Criteria

All subjects will require a chest X-ray and pulmonary function testing at screening, as defined in the Time and Events table. Subjects with clinical concern for pneumonitis will be evaluated per institutional practice with input from the GSK medical monitor. For management of suspected pneumonitis, including criteria for dose reduction and discontinuation of therapy, see Appendix 7.

To monitor for thrombocytopenia, CBCs will be drawn twice weekly for the first three weeks of study, weekly for the next two weeks, and then every other week, as described in the Time and Events table. Subjects who develop Grade 2 or greater thrombocytopenia may be monitored more frequently, as clinically indicated. Please see Appendix 7 for suggested management of thrombocytopenia.

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics). Deaths, SAEs, and Grade 3/4 adverse events will be carefully evaluated for the possibility of causality.

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, and/or if deaths related to study drug are observed, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded. The final determination will be made by the Sponsor and investigators.

The sponsor may also terminate the study if the safety, pharmacokinetics (PK) or pharmacodynamic (PD) data suggest that an appropriate therapeutic exposure cannot be achieved using the dosing schedules defined in the protocol.

5.5. Subject and Study Completion

A completed subject is one who has discontinued study treatment for reasons listed in Section 5.4 and completed a post-treatment follow-up visit or has died while receiving study treatment.

A subject will be considered to have completed the study 2 years after the last treatment or if the subject dies or is still receiving study treatment or in follow-up at the time the study is closed or terminated, whichever is sooner. Document the cause of death in the eCRF. The End of Study eCRF should only be completed when a subject is no longer being followed. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. GSK2820151

The term 'study treatment' is used throughout the protocol to describe the administration of GSK2820151.

	Study Treatment
Product name:	GSK2820151
Formulation description:	GSK2820151 capsules contain 1 mg, 5 mg, 10 mg, 50 mg, or 100 mg of GSK2820151 as free base equivalent
Dosage form:	Capsule
Unit dose strength(s)/Dosage level(s):	1 mg, 5 mg, 10 mg, 50 mg, and 100 mg
Route of Administration	Oral
Dosing instructions:	The dosing regimen is detailed in Table 7 and is designed to permit collection of detailed safety and PK data. • Week 1: Once daily on days 1, 3, 4, and 5 • Week 2: Once daily on days 1, 2, 3, 4, 5 • Weeks 3 and beyond: Once daily continuously GSK2820151 is to be administered orally, once daily, at approximately the same time of day, with no food or antacids for 1 h before and 2 h after each dose
Physical description:	1 mg: Pink, Size 1 capsule 5 mg: Green, Size 1 capsule 10 mg: Swedish Orange, Size 1 capsule 50 mg: White Opaque, Size 0 capsule 100 mg: Blue Opaque, Size 0 capsule

6.2. Treatment Assignment

Subjects will be assigned to receive GSK2820151 in an open-label fashion. There will be no placebo arm.

6.3. Packaging and Labeling

GSK2820151 will be provided to the sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated)

area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Laboratory Manual.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor or GSK study contact.

Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK2820151.

6.5. Compliance with Study Treatment Administration

At each visit, an evaluation of subject compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant subjects into compliance.

Compliance with GSK2820151 will be assessed through querying the subject during the site visits and documented in the source documents and case report form (CRF).

A record of the number of GSK2820151 tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.6. Treatment of Study Treatment Overdose

For this study, any dose of GSK2820151 greater than the protocol-specified dose within a 24 hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator (or treating physician) should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2820151 can no longer be detected systemically (at least 28 days for GSK2820151)
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.7. Treatment after the End of the Study

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) therapy at the discretion of the treating physician. New therapy should be documented on the CRF. Every effort should be made to complete the required withdrawal and follow up evaluations prior to initiating further therapy or dosing of an investigational agent (see Section 8.1 for follow-up assessments and procedures).

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

7. MEDICATION, DIETARY AND LIFESTYLE RESTRICTIONS

7.1. Concomitant Medications and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the Screening Visit until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, route of administration, dose and frequency of dosing, along with start and stop dates of administration should be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

7.1.1. Permitted Medications and Non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with erythropoietin, antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Colony-stimulating factors like filgrastim and pegfilgrastim may be used as clinically indicated. The only caveat is that subjects should not receive those medications listed as prohibited in Section 7.1.2.1.

Bisphosphonates will be allowed if subjects have been on a stable dose for at least three months prior to receiving the first dose of GSK2820151.

7.1.2. Prohibited Medications and Non-Drug Therapies

7.1.2.1. Prohibited Medications

The use of certain medications and illicit drugs within 5 half-lives or 28 days (if the drug is a potential enzyme inducer) prior to the first dose of study medication (and for the duration of the study) will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study treatment(s) is held, the GSK Medical Monitor can approve such use.

Subjects should not receive other anti-cancer therapy [including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormonal therapy (other than leuprolide or other LHRH agonists/antagonists), surgery or tumor embolization] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. Note, palliative radiation and/or surgical intervention may be permitted (for example to address pain management) and should be discussed with the GSK medical monitor prior to invention to determine appropriate dosing and schedule.

Anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc.) are PROHIBITED from seven days prior to the first dose of study drug through completion of the Final Study Visit. Low dose (prophylactic) anticoagulants are permitted provided that the subject's PT/PTT values meet entry criteria.

Subjects may continue to use aspirin, but doses are not allowed to be greater than 100mg per day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution, including concomitant use of proton pump inhibitors.

Co-administration of the medications listed in Table 5 are **PROHIBITED** for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of **amiodarone** which is prohibited beginning **6 months** prior to Screening through discontinuation from the study. [However, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines]).

Table 5 Drugs with a Risk of Torsades de Pointes that are Prohibited[1]

Amiodarone	Dronedarone	Moxifloxacin
Anagrelide	Droperidol	Papaverine
Azithromycin	Erythromycin	Pentamidine
Chloroquine	Escitalopram	Pimozide
Chlorpromazine	Flecainide	Procainamide
Cilostazol	Fluconazol	Propofol
Ciprofloxacin	Halofantrine	Quinidine
Citalopram	Haloperidol	Roxithromycin
Clarithromycin	Ibogaine	Sevoflurane
Cocaine	Ibutilide	Sotalol
Disopyramide	Levofloxacin	Sulpiride
Dofetilide	Levomepromazine	Sultopride
Domperidone	Levosulpiride	Terlipressin
Donepezil	Methadone	Thioridazine

Data Source: crediblemeds.org revision date 09 January 2017.

Drugs not available/used in the US have been omitted.

[1]The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (up to a maximum dose of 0.25 mg daily) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class (i.e. dolasetron and granisetron are not permitted).

7.1.2.2. Prohibited Non-Drug Therapies

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the screening visit through the post-study follow-up visit.

NOTE: Subjects may receive focal palliative radiation treatment during this study. Any proposed radiation therapy must be approved by the investigator and the GSK Medical Monitor prior to initiation.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit.

Herbal products include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto , ginseng.

The investigator should contact a GSK Medical Monitor before initiating treatment with any herbal preparation including marijuana.

7.1.3. Cautionary Medications

Co-administration of GSK2820151 and the following medications **requires EXTREME CAUTION** beginning **14** days prior to the first dose of study drug until discontinuation from the study, due to an increased risk of Torsades de Pointes. These medications include (but are not limited to):

Table 6 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution[1]

Alfuzosin	Foscarnet	Perphenazine
Apomorphine	Gemifloxacin	Pipamperone
Aripiprazole	Hydrocodone ER	Promethazine
Artenimole+piperaquine	Iloperidone	Rilpivirine
Asenapine	Imipramine	Risperidone
Atomoxetine	Isradipine	Saquinavir
Bedaquiline	Leuprolide	Sertindole
Buprenorphine	Lithium	Solifenacin
Clomipramine	Melperone	Tacrolimus
Clozapine	Mifepristone	Telavancin
Cyamemazine	Mirabegron	Telithromycin
Degarelix	Mirtazapine	Tetrabenazine
Delamanid	Moexipril/ hydrochlorothiazide	Tiapride
Desipramine	Nicardipine	Tizanidine
Dexmedetomidine	Norfloxacin	Tolterodine
Efavirenz	Nortriptyline	Trimipramine
Ezogabine	Ofloxacin	Tropisetron
Famotidine	Oxytocin	Vardenafil
Felbamate	Paliperidone	Venlafaxine
Fingolimod	Pasireotide	Zotepine
Flupentixol	Perflutren lipid microspheres	Perphenazine

Data Source: crediblemeds.org revision date 09 January 2017.
[1]The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject
Drugs not available/used in the US have been omitted

After starting cautionary medications such as in Table 6, it is recommended that ECGs are implemented daily until the steady state of the new medication is reached. If there are ECG abnormalities, implement additional cardiotoxicity monitoring as addressed Appendix 7.

There is a low potential for GSK2820151 to induce or inhibit cytochrome P450 (CYP) enzymes. GSK2820151 has been demonstrated to inhibit Breast Cancer Resistance Protein (BCRP [IC_{50}=3.6 μM]) and thus may alter the metabolism of medications that are substrates of BCRP. These medications include 3-hydroxy-3-methyl-glutaryl-coenzyme

A reductase (HMG-CoA) reductase inhibitors (statins) as well as ciprofloxacin and other fluoroquinolones (though not levofloxacin).

Furthermore, GSK2820151 inhibits P-glycoprotein (PgP) at concentrations ≥ 100 μM. PgP substrates include medications such as statins and digoxin, which may have a narrow therapeutic index. While co-administration of these agents with GSK2820151 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

GSK2820151 may also interact with organic anion transporter 3 (OAT3). Substrates of OAT3 include agents such as Penicillin G and indomethacin. While co-administration of these agents with GSK2820151 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

7.2. Dietary Restrictions

GSK2820151 will be administered under fasting conditions, with no food or antacids for 1 h before and 2 h after each dose. Requirements for fasting before and after dosing may be modified based on available pharmacokinetics (PK), pharmacodynamics (PD) and safety data. Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted. Subjects will be instructed to record the time and date of study treatments and meals in relation to dosing in the supplied GSK dosing diary.

Subjects will abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final PK and or PD sample during each serial PK sampling day (e.g., Days 1 and 18).

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment until the last dose of study drug.

On serial PK sampling days, subjects enrolled in the serial PK cohort should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.

7.3. Lifestyle Restrictions (Contraception)

7.3.1. Female Subjects

Female subjects of childbearing potential must not become pregnant during the trial and for 7 months after stopping study medication and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of ≤ 1%.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of ≤ 1%

- Non-hormonal intrauterine device (IUD) or intrauterine system (IUS) that meets the ≤1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

All hormonal means of birth control such as oral, injectable, dermal, subdermal or topical contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

7.3.2. Male Subjects

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment and until 16 weeks after the last dose of study drug.

- Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview, **OR**
- Condom use PLUS partner use of a highly effective contraceptive (≤1% rate of failure per year) such as occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/film/cream/suppository), or intrauterine device. **OR**
- Condom use PLUS partner use of hormonal birth control such as contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches.

The above list does not apply to male subjects with a female partner of child bearing potential who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic

abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception

In addition, male participants must refrain from donating sperm for duration of study and until 16 weeks after the last dose of study drug.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 8.1

8.1. Time and Events Tables

Table 7 Time and Events

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X	X	X			X	X	X	X	X			Daily									
Review subject diary	Diary not required when dosed in clinic.									X							X		X		X	X	X	X		
Safety																										
Pregnancy test/ testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																						EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp, O2 saturation	X	X	X				X		X					X		X		X		X	X	X	X		X
Pain (using Wong-Baker Faces Pain Rating scale)		X	X	X				X		X					X		X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function tests (spirometry, Diffusing capacity of the lungs for carbon monoxide [DLCO], and room air O2 saturation at rest via pulse oximetry)	All patients will have PFTs at baseline; afterwards as clinically indicated (e.g., in patients with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage and chest radiation etc)	X																								
Adverse events		*continuous from signing of informed consent*																								
Concomitant medications		*continuous from signing of informed consent*																								
Laboratory assessments: For details please see following tables																										
Tests		X	X	X				X		X					X		X		X		X	X	X	X	X	X
Cardiac Monitoring																										
Echocardiogram	Within 35 days of first dose	X																			X		X		X	X
12-lead ECGs	Triplicate SCR ECGs within 35	X	O	O	X		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
(Triplicate)	days of first dose. For timing of triplicate ECGs on O days, see Table 9 and Table 10. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.			X																						
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X	X				X						X					X						X		
Telemetry	Start at least 60 min predose and for at least 48 h.		X	X																						
Efficacy																										
Cross-sectional (Computed tomography [CT] or magnetic resonance imaging [MRI]), functional (Positron emission tomography [PET]), or nuclear (bone scan) imaging	Appropriate imaging modality should be selected by the investigator depending on disease histology and location. SCR assessment within 2 weeks of first dose. Target lesions to be identified at SCR and followed. See Section 14.8.1 for guidelines.	X																					X		X	X
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see Table 9 and Table 10																										
PK and biomarker samples			X	X			X						X					X						X		
Samples for		X	X	X														X								X

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
mRNA																										
LPS blood sample			X																							
PK Urine samples			X															X								
Pharmacogenomics (PGx)																										
PGx sample			X																							
FOLLOW-UP PHASE																										

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death.

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; O= For timing of triplicate ECGs on O days, see Table 9 and Table 10; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; W=week

Table 8 Time and Events: Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	W1			W2		W3	W4	W5	W7	W9	q4W	q8W	EOT
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP-9	W1D1, W1D2: local lab sample 3X/24h; central lab sample 1X/24h. All other timepoints including unscheduled collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X	X		X		X	X
Hematology		X	X		X	X	X	X[1]	X	X	X	X	X		X
Clinical chemistry		X	X		X	X	X	X	X	X	X	X	X		X
Pancreatic		X	X		X	X		X		X	X	X	X		X
Coagulation		X	X		X	X		X		X	X	X	X		X
Factor VII Assay	Also perform if PT, INR or aPTT are ≥1.5XULN, or in case of bleeding event	X						X		X					
Creatine phosphokinase		X	X		X	X		X		X	X	X	X		X
Liver chemistry		X	X		X	X	X	X	X	X	X	X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X	X		X		X	X	X	X		X
c-peptide and 1,5 –Anhydroglucitol (1,5 AG)	Will be performed at central lab if not available at local lab	X	X							X		X		X	
Hemoglobin A1c		X	X							X		X		X	
Fasting lipids		X	X							X		X		X	X
Thyroid monitoring	Thyroid stimulating hormone (TSH), free T3, free T4. If TSH is abnormal at W1D1, continue monitor TSH, free T3 and free T4 going forward	X	X							X		X		X	X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Urinalysis		X	X							X		X		X	X
Pregnancy test, females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X							X		X	X		X
Testosterone, males	Complete and free testosterone at SCR; free testosterone thereafter	X	X							X		X	X		X
CK, CK-MB	Predose and 12-18 h post dose		X	*as clinically appropriate*											
Safety Cytokines	This is collected as part of the Predose PK sample and is sent to Myriad via Covance.	X	*as clinically appropriate following fever*												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X													

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

1. If any parameter (i.e., platelets) shows a downward trend, additional analyses should be performed within 2-3 days to monitor.

Table 9 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1										**W1D5**		**W2D4 + 1 day**			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±2h**	**24h ±2h**	**33h ±3h**	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**
12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sampling	X	0-2h			2-24h											
mRNA whole blood sample	X				X	X	X		X	X						
LPS whole blood sample	X	X	X	X	X	X										

Plasma samples will be divided at the site into two, one sample will be shipped to GSK DMPK facility where bioanalysis of PK is performed and the second sample will be sent via Covance to Myriad for systemic cytokine assessment and acute phase protein assessment. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed. .

On serial PK sampling days, subjects enrolled in the serial PK cohort should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days (+2 to +7 days for alternate dosing schedule)										**W9D1 +4 days** (if dose has been escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±4h**	**24h ±1h**	**48h ±1h**	**pre dose**	**0.5-2h**	**4 - 8h**	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine PK sampling		0-2h			2-24h									
mRNA whole blood sample	X													X
LPS whole blood sample														

Plasma samples will be divided at the site into two, one sample will be shipped to GSK DMPK facility where bioanalysis of PK is performed and the second sample will be sent via Covance to Myriad for systemic cytokine assessment and acute phase protein assessment. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

On serial PK sampling days, subjects enrolled in the serial PK cohort should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

8.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race, and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

8.2.1. Critical Baseline Assessments

The following are required at baseline:

- imaging (e.g., CT of the Chest/Abdomen/Pelvis or MRI of the Abdomen/Pelvis) at the discretion of the investigator, based on the subject's disease. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required.
- cardiology evaluation including echocardiogram, 12-lead ECG and Holter monitoring

8.2.2. Visit Windows

Screening (baseline to pre-dose): All assessments should be completed within 14 days prior to screening. Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Week 1: Based on subject and clinic schedule, Week 1 Day 3 assessments can be ± 1 day.

Week 2 to Week 9: Based on subject and clinic schedule, assessments can be ±3 days.

Monthly visits after Week 9 until Week 52: After the first disease assessment has been completed then the month clinic visits can be scheduled ± 5 days.

Monthly visits after Week 52: clinic visits can be scheduled ± 7 days.

Discontinuation visit: should be 14 days from last dose of study drugs. If a subject is unable to return to the clinic due to hospitalization, site staffs are encouraged to telephone the subject for assessment of adverse events.

8.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 8.1). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Note that this section details the procedures used to evaluate for safety and toxicity for this study. For management and recording of any suspected Adverse Events, refer to Section 9, Appendix 6 and Appendix 7.

8.3.1. Physical Exams

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses

8.3.2. ECOG Performance Status

The performance status will be assessed using the ECOG scale (Appendix 2) as specified in the Time and Events Table (Section 8.1).

8.3.3. Vital Signs

- Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
    - In case of an abnormal first reading, three readings of blood pressure and pulse rate should be taken, the first reading should be rejected and the second and third averaged to give the measurement to be recorded in the CRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

Refer to the Study Reference Manual (SRM) for details regarding measurement of vital signs.

8.3.4. Pain

Pain will be assessed using Wong-Baker Faces Pain Rating scale (Appendix 11).

8.3.5. Echocardiogram

For all subjects, trans-thoracic echocardiograms (TTEs) will be performed at screening and at assessment times as outlined in Table 7. TTEs should be evaluated and compared to baseline by the same reader.

ECHO data may be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying ECHO scans are provided in the Study Procedure Manual (SPM) .

8.3.6. Safety Electrocardiograms (ECG)

Safety ECGs will be performed at the time points specified in Table 7 using a standard 12-lead ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Details will be provided in the SPM.

8.3.6.1. Routine ECG Monitoring

Triplicate 12-lead ECGs should be performed at Screening and at all other time points, including on Serial Pharmacokinetic sampling days.

Standard 12-lead ECGs (Safety ECGs) will be performed as part of the real-time assessment of subjects and may not be included in the primary QT analysis. Safety ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

ECG data may be transferred and reviewed by an independent central reviewer. Instructions for submission of ECGs are provided in the SPM.

8.3.6.2. Evaluation of QTc

All ECGs must include QTcF measurements. For the definition of QTcF and management strategies for QTcF ≥ 500 msec, see Section 5.4.2 and Appendix 7.

8.3.7. Telemetry

In addition to Safety ECG assessments, monitoring for potential adverse arrhythmias will be conducted utilizing continuous inpatient telemetry monitoring as outlined in Table 7 for at least 48 hours from the start of the first dose. If clinically indicated, telemetry may be extended past 48 hours. Participating sites will have trained staff capable of monitoring and responding in real time to any potential cardiac adverse event detected by telemetry. In addition, emergency resuscitation equipment including appropriate pharmacological agents will also be immediately accessible.

8.3.8. Holter Monitoring

In addition to the Safety ECGs performed during the study, continuous 12-lead ECGs (obtained via a Holter monitor) will be acquired while subjects are at the site. Dual snap electrodes will be utilized to enable simultaneous collection of Holter and safety ECG data.

Digital Holter ECG data will be obtained from 12-lead continuous Holter monitoring device supplied by the Sponsor. ECG acquisition via the Holter monitoring device will be performed at planned time points indicated in the Time and Events and should be obtained prior to phlebotomy and vital sign time points.

Collection of critical ECG data shortly after meals or during sleep should be avoided since QT prolongation occurs at these times and a change in the QT-RR relationship occurs during sleep. Meals should be administered according to the guidelines provided in Section 7.2 and in the Laboratory Manual as meal and snack times will need to be adjusted accordingly on dosing and ECG sampling days.

Analysis of intervals and morphology from the continuous digital ECG data will be acquired and stored electronically and manually over-read by an external central validated ECG laboratory. Around each of the designated time points, 3 ECGs will be selected approximately 2 minutes apart. In order to increase consistency of ECG interpretation, a limited number of central ECG over-readers will be used throughout the study. All ECGs for a given subject will be over-read by the same reader from the central validated ECG laboratory. The central reader will be blinded to subject identifiers (e.g., subject number, age, and sex), treatment assignment, and study day when Holter data were collected. The final intervals and morphology analyses entered into the database will be those generated by the central ECG laboratory.

QT/QTcF values will be determined using time matched ECGs obtained from the Holter monitor on following time points: screening, Week 1 Day 1; Week 1 Day 5, Week 2 Day 4 and Week 3 Day 4 and Week 9 Day 1. The mean from triplicate ECGs will be evaluated at each time point. For a given time point, the mean QTcF from 3 separate beats should be analyzed on each ECG. Analysis of Lead II will be conducted with V5 as back-up and one of the remaining precordial leads as an alternative when T waves are not well defined in Leads II or V5. QTcF for an individual beat will be calculated from the preceding RR interval since using the average heart rate (RR) intervals from the ECG could result in inaccurate QTcF calculations due to beat to beat variations in the RR intervals.

QT values should not be reported when the rhythm is other than sinus rhythm (sinus rhythm with normal respiratory variation is acceptable), and in intraventricular conduction delays (IVCD, QRS >120 msec). The other ECG information (including the rhythm and presence of IVCD) should be reported. The choice of the 3 consecutive beats to be measured should avoid ectopic beats and the first beat after an ectopic beat. If IVCD occur, these should be reported.

8.3.9. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 11, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All protocol required safety laboratory assessments, as defined in Table 11, are performed at the institution's local laboratory. All non-safety assessments (e.g., pharmacokinetic samples and translational samples) will be assessed by a central laboratory. Please refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Some laboratory assessments (e.g., testosterone) can vary throughout the day. It is recommended but not mandated that laboratory assessments are collected at approximately the same time on each clinic day. If abnormal testosterone levels are observed, repeat measurements should occur at the approximate baseline timing to ensure this is a trend and not a single outlying event.

Table 11 Clinical Laboratory Tests

Serum Chemistry			
Blood urea nitrogen	Magnesium	aspartate aminotransferase	Total and direct bilirubin
Sodium	Potassium		Uric acid
Creatinine	Chloride	alanine aminotransferase	Albumin
Fasting Glucose	Total carbon dioxide	alkaline phosphatase	Total protein
Creatine phosphokinase	Ionized calcium	gamma-glutamyltransferase	Total calcium
Hematology			
Platelet count	*Automated White Blood Cell*		
Red blood cell count	*Differential:*		
White blood cell count (absolute)	Neutrophils (absolute)		
Hemoglobin	Lymphocytes (absolute)		
	Monocytes (absolute)		
	Eosinophils (absolute)		
	Basophils (absolute)		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Tests			
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)			
Pancreatic markers (amylase and lipase)			
Fasting Lipid panel (triglycerides and total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])			
C-Peptide			
Troponin (I or T at local laboratory, Troponin T at central laboratory]			
Insulin			
Hemoglobin A1C			
1,5 –Anhydroglucitol (1,5 AG)			
NT-proBNP			
Thyroid-stimulating hormone (TSH)			
Free Thyroxine 3 (Free T3)			
Free Thyroxine 4 (Free T4)			
Creatine kinase (CK)			
Creatine Kinase-MB isoenzyme (CK-MB)			
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose)			
Pregnancy test for females (serum at screening, Urine or serum post dose)			
Cytokine samples			

Subjects should be instructed to fast (no food and only water allowed) for 10 hours prior to any fasting laboratory assessments (e.g., fasting glucose, fasting lipid panel, etc.).

All laboratory results that are considered by the investigator clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be recorded on the eCRF as AEs. In addition, these clinically significant abnormal laboratory results should be followed until the abnormality resolves or is determined to be stable. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.3.10. Troponin Measurement

. At W1D1 and W1D2 three local lab troponin samples (8hrs apart) should be drawn per day but only 1 central lab sample should be drawn per day. At other time-points (including unscheduled visit) only two samples should be drawn; 1 for local lab analysis and 1 for central lab analysis. Troponin T will be assessed at a central laboratory as a means of consistent evaluation across all subjects Whereas second sample, assessed at a local laboratory, will be used for purpose of subject management. Whenever possible, troponin T will be assayed by the local laboratory. However, either troponin I or troponin T may be assessed at a local laboratory. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study.

8.3.11. Pregnancy

- Reporting of any pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until 7 months following the last dose of GSK2820151.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Details on follow-up procedures outlined in Appendix 7.

8.4. Pharmacokinetics

PK analyses will be the responsibility of GSK Clinical Pharmacokinetics Modeling & Simulation (CPMS). Plasma GSK2820151 concentration-time data will be analyzed by non-compartmental methods with WinNonlin.

From the plasma concentration-time data, the following pharmacology parameters will be determined, as data permit: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve ($AUC_{(0-\tau)}$ and $AUC_{(0-\infty)}$ Week1 Day1 only) and apparent terminal phase half-life ($t_{½}$). Trough concentration ($C\tau$) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined from the ratio of $AUC_{(0-\tau)}$ in Week 3 Day 4 / $AUC_{(0-\tau)}$ in Week 1 Day 1. The ratio of AUC(0-τ) on Week 3 Day 4/ Week 1 Day 1 AUC(0-∞) will be calculated to assess time invariance. GSK2820151 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

Plasma concentration-time data will be listed by dose and summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) PK parameters values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters [if applicable]) by dose cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are evaluated, dose proportionality of AUC and Cmax for GSK2820151 will be assessed using the power model (details will be provided in the Reporting and Analysis Plan [RAP]).

Plasma concentration-time data will be further analyzed using appropriate model(s) to determine population PK parameters (absorption rate (Ka), apparent clearance (CL/F) and volume of distribution (V/F)) and summary exposure measures (Cmax, AUC and Average observed concentration [Cav] = AUC/τ) and identify important covariates (e.g., age, weight, or disease related covariates).

8.4.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of GSK2820151 will be collected at the time points indicated in the Time and Events Schedule (Table 9 and Table 10).

Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded along with the date and time of the prior dose administration. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. This will not require a protocol amendment. In addition, plasma samples may be analyzed qualitatively for other circulating compound-related material and the results will be reported under a separate Drug Metabolism and Pharmacokinetics (DMPK) protocol.

Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

8.4.2. Urine Sample Collection for Pharmacokinetics

Urine samples for quantitative analysis of GSK2820151 will be collected over 24 hours in two samples (sample collected 0-2 hr and a second sample collected 2-24 hr) immediately following dosing on Week 1 Day 1 and Week 3 Day 4

The actual date and time of each urine sample collection will be recorded. In addition, pooled urine pH, the total volume of the pooled urine and the weight of the pooled urine will be measured and recorded in the eCRF.

Details of urine sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

8.4.3. Pharmacokinetic Sample Analysis

Plasma sample analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics (DMPK), Platform Technology and Science (PTS), GlaxoSmithKline. Concentrations of GSK2820151 will be determined in plasma samples using the currently approved bioanalytical

methodology. Raw data will be stored in the Good Laboratory Practices (GLP) Archives, GlaxoSmithKline.

Once the plasma samples have been analyzed for GSK2820151, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

Urine sample analysis may be performed under the management of Bioanalytical Science and Toxicokinetics, DMPK, PTS, GlaxoSmithKline. Concentrations of GSK2820151 may be determined in urine samples using an investigative analytical methodology. Urine raw data will be stored in the GLP Archives, GlaxoSmithKline.

The urine samples may be analyzed for compound-related metabolites and the results will be reported under a separate DMPK protocol.

8.5. Pharmacokinetic/Pharmacodynamic Analysis

Observed or predicted concentrations and/or exposures will be combined with safety, efficacy, and/or PD measures of interest to examine potential exposure response relationships.

The relationship between QTcF and concentration expressed as Cmax, Cav, and instantaneous time-matched concentration will be plotted graphically. A linear mixed effects analysis of the slope of the QTcF-concentration responses adjusting for baseline will be evaluated as a means of estimating QTcF effect in lieu of a thorough QT study.

Other quantitative safety parameters and biomarkers of interest including changes in troponin levels will be plotted graphically against summary exposure measures (e.g., Cmax, Cτ, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PK/PD parameters of interest; slope, baseline (E0), exposure producing 50% of the maximum effect (EC_{50}), and maximum effect (Emax).

Overall efficacy data and overall tumor burden may be described using ordered categorical model and continuous models with summary exposure parameters (e.g., Cmax, Cτ, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the RAP.

8.6. Efficacy

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per RECIST 1.1.

- Lesion assessment will be conducted according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009] as outlined below and in Appendix 8.

- Disease assessment modalities may include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions).
- The baseline disease assessment will be completed within 2 weeks prior to the first dose of GSK2820151, then every 8 weeks starting W1D1 thereafter, and at the final study visit. See the Time and Events Table (Section 8.1) for the schedule of assessments of anti-cancer activity.
- For subjects with CRPC without measurable disease by RECIST criteria, serial prostate specific antigen (PSA) measurements will be drawn at the disease assessment time points defined in the Time and Events Table (Section 8.1). Response will be defined by the number of subjects who achieve a 50% decrement in their baseline PSA (PSA50).
- Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.
- Subjects whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator.
- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

8.7. Translational Research

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be addressed in the RAP.

8.7.1. Biologic Effects of GSK2820151

Exploratory analysis may be performed to examine potential relationships between drug exposure and markers of BET target inhibition (e.g., cytokines, acute phase proteins, relevant transcripts, and/or proteins) or between anticancer activity and potential markers of sensitivity (e.g., genetic alterations).

8.7.2. RNA Expression Research

Related BET inhibitors have been shown to modulate the expression of a number of different genes in unstimulated whole blood between 1 h and 6 h. The mRNA levels of 31 such genes form a 'signature' panel which will also be used as a biomarker of engagement of pharmacology and will be measured using mRNA isolated from whole

blood. The modulation of a number of these genes will also be measured as changes in systemic proteins as well as in the analysis of the ex vivo assay blood samples (e.g., Chemokine [C-C motif] ligand 2 [CCL2] and Interleukin 8 [IL-8]) thus relating mRNA and protein expression with drug concentration. Other translational research studies, such as transcriptomics profiling, will also be performed using whole blood mRNA from selected patients.

8.7.3. Effects of GSK2820151 on Systemic Markers of Inflammation

GSK2820151 has been shown to inhibit LPS-induced IL-6 across different human cell populations and species. The action of the compound is through inhibition of the assembly of transcriptional complexes required to express the protein. Pre-clinical studies demonstrate that blood concentration of drug correlates to the degree of inhibition of LPS induced IL-6 in ex vivo whole blood samples. Therefore, this biomarker will be used as an indication of pharmacology and will be aligned with PK sampling. Since inhibition of BET family proteins is known to inhibit a range of pro-inflammatory mediators and acute phase proteins, a number of additional proteins (46) will also be measured from these ex vivo samples.

The set of analytes identical to that used in the whole blood ex vivo assay (including for example, CCL2, macrophage inflammatory protein 1 alpha [MIP1-α], IL-8) will also be measured in plasma samples taken during PK sampling and at the time of any Grade 2 fever or symptoms indicative of a potential cytokine storm. This will assess systemic inflammatory response in the subject using biomarkers such as pro-inflammatory cytokines and acute phase proteins and correlate the systemic response to drug with that in stimulated and unstimulated blood. These biomarkers are expected to change over days rather than hours, based on the plasma half lives and pre-clinical data, such that sampling will also be performed after repeat dosing.

8.8. Pharmacogenetic Analysis

An important objective of the clinical study is pharmacogenetic (PGx) research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in host deoxyribonucleic acid (DNA) from blood will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics, and efficacy) to treatment with GSK2820151.

Information regarding pharmacogenetic research is included in Appendix 5. In approving the clinical protocol, the independent ethics committee/institutional review board (IEC/IRB) (and, where required, the applicable regulatory agency) also approve the PGx assessments unless otherwise indicated. Where permitted by regulatory authorities, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated.

When PGx assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

Information regarding genetic research is included in. Appendix 5

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DATA COLLECTION, REPORTING, AND FOLLOW-UP

9.1. Definition of AE/SAE

The definitions of an AE or SAE can be found in Appendix 6. The severity of adverse events will be graded utilizing the NCI-CTCAE v4.03. Additional details regarding management of specific AEs or SAEs are described in Appendix 7.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

9.1.1. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 6 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.1.2. Other Sentinel Events

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

9.1.3. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

NOTE: If either of the following conditions apply, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

9.2. Time period and Frequency for collecting AE and SAE information

- At each visit/contact, AEs and SAEs will be collected from the first dose (start of Study Treatment) until 28 days after the last dose of study treatment or until the start of new anti-cancer therapy-whichever occurs first.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 6

9.2.1. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"

- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

9.2.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 6.

9.2.3. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

10. DATA MANAGEMENT

For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

11. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

11.1. Hypotheses

The primary endpoints of this study are safety and tolerability; the MTD and RP2D will also be determined. No formal statistical hypotheses will be tested. The primary focus will be on determining the recommended dose for further exploration, the safety profile, and the PK of GSK2820151 in subjects with advanced cancer. Analyses will be descriptive and exploratory.

11.2. Continual Reassessment Method

11.2.1. Description of Continual Reassessment Method

After all subjects in each cohort have completed the DLT observation period, a dosing recommendation for the next cohort will be made following an N-CRM analysis. All available data, including safety and PK data from current and prior cohorts will be reviewed at the dose escalation meeting. Although the N-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor in consultation with the study team and Investigators, and taking into account PK and PD data, will determine dose escalation as deemed appropriate.

The N-CRM design makes use of a Bayesian logistic regression model relating dose and toxicity and is expected to locate the MTD efficiently while minimizing the number of subjects exposed to pharmacologically inactive or unsafe dose levels.

The MTD will be defined as that dose that has the highest posterior probability of having a DLT rate within the Target Toxicity range and for which the posterior probability that the DLT rate lies within the Excessive Toxicity or the Unacceptable Toxicity range is less than 25%.

The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- A dose falls in the **Under-dosing** range if the probability of a DLT at the dose is 0% - 16%
- A dose falls in the **Target** Toxicity range if the probability of a DLT at the dose is 16% - 33%
- A dose falls in the **Excessive** Toxicity range if the probability of a DLT at the dose is 33% - 60%
- A dose falls in the **Unacceptable** Toxicity range if the probability of a DLT at the dose is 60% - 100%

An updated posterior estimate of the dose-toxicity curve will also be provided at the time of the dose-escalation meeting.

11.2.1.1. Implementation of N-CRM

The N-CRM model implementation will be performed using the Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 2.3 or higher) software from Tessella.

11.2.1.2. Bayesian Prior

The N-CRM methodology requires that a Bayesian prior distribution for the dose-toxicity curve be pre-specified. The Bayesian prior used for this design was determined using the quantile method. For each dose, the most likely (median) presumed probability of DLT was specified, along with a 95% credible interval – an interval within which the team is 95% a priori certain the probability of a DLT lies. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK2820151 in humans and to allow the accumulating data to have more influence on dose recommendations than the prior. Further details regarding the specific N-CRM model will be provided in the Reporting and Analysis Plan (RAP) and will be determined before the first dose-escalation meeting after consideration of all information gathered before then.

11.3. Sample Size Considerations

11.3.1. Sample Size Assumptions

The total number of subjects to be enrolled into this study will depend on the number of subjects needed to characterize individual dose cohorts for the determination of the maximum tolerated dose of GSK2820151; the final sample size is not driven by statistical considerations. However, it is anticipated that approximately 30 to 50 subjects will be enrolled with a maximum of 80 subjects.

11.3.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

11.4. Data Analysis Considerations

Data will be listed and summarized according to GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

11.4.1. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2820151. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **PK Population** will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

Additional analysis populations may be defined in the RAP.

11.4.2. Interim Analysis

Interim analyses will be performed to determine if a dose-escalation is appropriate. The primary driver for the dose-escalation decisions will be safety and tolerability of each dose cohort.

If this trial enrolls more than 20 patients at the recommended phase 2 dose (RP2D), an interim analysis for futility and complete review of safety data will be performed on first 20 patients treated. This analysis will be used to evaluate the risk-benefit of continued treatment of these patients and to assess the risks related to delayed GSK2820151-related toxicities.

An interim analysis of the pharmacodynamic data will be conducted once an appropriate amount of data has been collected and has been batched for analysis. Interim analyses of the pharmacodynamic data may be conducted throughout the duration of the study.

11.5. Key Elements of Analysis Plan

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

All data will be summarized and listed.

11.5.1. Primary Analyses

As the primary endpoints of this study are safety and tolerability, the primary analyses will be descriptive in nature. Safety endpoints are described in Section 5.4.

The All Treated Population will consist of all subjects receiving at least one dose of study drug and will be used for the analysis of safety and efficacy data. Complete details of the analyses will be provided in the RAP.

11.5.2. Secondary Analyses

11.5.2.1. Pharmacokinetic Analyses

11.5.2.1.1. Pharmacokinetic Parameters

PK analyses will be the responsibility of CPMS, GSK. Plasma GSK2820151 concentration-time data from dose escalation will be analyzed by non-compartmental methods with WinNonlin.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC(0-t) and AUC(0-∞) Week1 Day1 only) and apparent terminal phase half-life (t½). Trough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined. The ratio of AUC(0-τ) on Week 3 Day 4 AUC(0-τ) / Week 1 Day 1 AUC(0-∞) will be calculated to assess time invariance. GSK2820151 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

11.5.2.1.2. Statistical analysis of pharmacokinetic parameters

Statistical analyses of the PK parameters data will be conducted by Clinical Statistics, GSK. Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) pharmacokinetic parameter values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters [if applicable]) by dose cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data),dose proportionality of AUC and Cmax for GSK2820151 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

11.5.2.2. Efficacy Analysis

For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR, or stable disease) prior to the initiation of therapy. Progressive disease (PD) will also be defined per RECIST 1.1 criteria. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. PFS will be summarized using Kaplan-Meier methods.

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per RECIST 1.1 criteria. Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. Exact methods for calculated confidence intervals will be given in the RAP.

The number and types of responses, as outlined in RECIST 1.1, will be listed and summarized, as appropriate.

11.5.2.3. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, electrocardiogram [ECGs]) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

11.5.2.4. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy

11.5.2.5. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE v4.03.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE v4.03, will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Dose-limiting toxicities (DLTs) will be listed for each subject and summarized by dose cohort.

AEs of special interest will be outlined in the RAP.

The incidence of deaths and the primary cause of death will be summarized.

11.5.2.6. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4.03. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Further details will be provided in the RAP.

11.5.3. Other Analyses

Exploratory analyses may be performed to examine potential relationships between anticancer activity and changes in markers of BET target inhibition or tumor biology

(e.g., cytokines, acute phase proteins, relevant transcripts, and/or proteins) or between anticancer activity and potential markers of sensitivity.

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details on the translational research analyses will be addressed in the RAP.

12. STUDY GOVERNANCE CONSIDERATIONS

12.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

12.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is

being deferred and the study, with the exception of the optional assessments, can be initiated.

12.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

12.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

12.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where

applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

12.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

12.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

13. REFERENCES

Asangani IA, Dommeti VL, Wang X, Malik R, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature. 2014; 510(7504): 278-82.

Bauer DE, Mitchell CM, Strait KM, Lathan CS, et al. Clinicopathologic Features and Long-term Outcomes of NUT Midline Carcinoma. Clin CanRes. 2012; 18:5773-9.

Chaidos A, Caputo V, Gouvedenou K, Liu B, Liu B, et.al. Potent antimyeloma activity of the novel bromodomain inhibitors I-BET151 and I-BET762. Blood 2014; 123(5): 697-705.

Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976; 16: 31-41.

Delmore JE, Issa GC, Lemieux ME, Ral PB, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011; 146: 904-917.

Dey A, Chitsaz F, Abbasi A, Misteli T, Ozato K. The double bromodomain protein Brd4 binds to acetylated chromatin during interphase and mitosis. Proc Natl Acad Sci U S A. 2003;100(15): 8758-63.

Dey A, Nishiyama A, Karpova T, McNally J, Ozato K. Brd4 marks select genes on mitotic chromatin and directs postmitotic transcription. Mol Biol Cell. 2009; 20(23): 4899-909.

Dhalluin C, Carlson JE, Zeng L, He C, et. al. Structure and ligand of a histone acetyltransferase bromodomain. Nature 1999; 399: 491–496.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, et al. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). Eur J Cancer. 2009; 45: 228-247.

Fiskus W, Sharma S, Qi J, Shah B, et al. BET Protein Antagonist JQ1 Is Synergistically Lethal with FLT3 Tyrosine Kinase Inhibitor (TKI) and Overcomes Resistance to FLT3-TKI in AML Cells Expressing FLT-ITD. Mol Cancer Ther. 2014; 13(10); 2315–27.

French C, Ramirez C, Kolmakova J, Hickman TT, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene, 2008; 27: 2237-42.

GlaxoSmithKline Document Number 2014N208278_00; GSK2820151 Investigator's Brochure. Version 1. 13-JAN-2015

Hargreaves DC, Horng T, Medzhitov R. Control of inducible gene expression by signal-dependent transcriptional elongation. Cell. 2009; 138(1): 129-45.

Itzen F, Greifenberg AK, Bösken CA, Geyer M. Brd4 activates P-TEFb for RNA polymerase II CTD phosphorylation. Nucleic Acids Res. 2014; 42(12): 7577-90.

James LP. 2009. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Disp. 2009; 37: 1779-1784.

Jang MK, Mochizuki K, Zhou M, Jeong HS, Brady JN, Ozato K. The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription. Mol Cell. 2005; 19(4): 523-34.

Mertz J, Conery AR, Bryant BM, Sandy P, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Nat Acad Sci. 2011; 108: 16669-74.

NCI-CTCAE (NCI Common Terminology Criteria for Adverse Events), Version 4.03, DCTD, NCI, NIH, DHHS, June 14, 2010.

Neuenschwander B, Branson M, and Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008 27: 2420–39.

Nicodeme E, Jeffrey K, Schaefer U, Beinke S, et al. Suppression of inflammation by a synthetic histone mimic. Nature 2010; 478: 1119-1123.

NYHA, 1994; The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group, 1982.

Paillisson A, Levasseur A, Gouret P, Callebaut I, Bontoux M, Pontarotti P et al. Bromodomain testis-specific protein is expressed in mouse oocyte and evolves faster than its ubiquitously expressed paralogs BRD2, -3, and -4. *Genomics*, 2007;89: 215-23.

Patel MC, Debrosse M, Smith M, Dey A, et.al. BRD4 coordinates recruitment of pause release factor P-TEFb and the pausing complex NELF/DSIF to regulate transcription elongation of interferon-stimulated genes. Mol Cell Biol. 2013; 33(12): 2497-507.

Trabucco SE, Gerstein RM, Evens AM, Bradner JE, et al. Inhibition of bromodomain proteins for the treatment of human diffuse large B-cell lymphoma. Clin Cancer Res. 2014 Jul 9. Pii: clincanres.3346.2013. [Epub ahead of print]

Trousdale RK and Wolgemuth DJ. Bromodomain containing 2 (Brd2) is expressed in distinct patterns during ovarian folliculogenesis independent of FSH or GDF9 action. Molecular *Reproduction and Development*, 2004;68:261-8.

Wyce A, Ganji G, Smitheman KN, Chung CW, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PloS One 2013;8:e72967.

Yan J, Diaz J, Jiao J, Wang R, You J. Perturbation of BRD4 function by BRD4-NUT abrogates cellular differentiation in NUT midline carcinoma. J Biol Chem. 2011; 286:27663-27675.

14. APPENDICES

14.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

°C	Degrees Celsius
1,5 AG	1,5 –Anhydroglucitol
A1c	Glycosylated hemoglobin
ACLS	Advanced Cardiac Life Support
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-∞)	Area under the curve from zero to infinity
AUC(0-24)	Area under the curve from zero to 24 hours
AUC(0-τ)	Area under the plasma concentration-time curve
BAL	Bronchoalveolar lavage
BCRP	Breast Cancer Resistance Protein
BET	Bromodomain & extra-terminal
BID	Twice daily
BP	Blood pressure
BPM	Beats per minute
BRD	Bromodomain
Cav	Average observed concentration
CBC	Complete blood count
CCL2	Chemokine (C-C motif) ligand 2
CK	Creatine kinase
CK-MB	Creatine kinase MB isoenzyme
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
COPD	Chronic obstructive pulmonary disease
CPMS	Clinical Pharmacokinetics Modeling & Simulation
CR	Complete response
CRC	Colorectal cancer
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
C_τ	Trough concentration
CV	Cardiovascular
CV%	Percentage coefficient of variance
DHEA	Dehydroepiandrosterone

dl	Deciliter(s)
DLT	Dose-limiting toxicity
DLCO	Diffusing capacity of the lungs for carbon monoxide
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EC50	Exposure producing 50% of E_{max}
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic case report form
EFD	Embryo-fetal development
EIAC	Enzyme-inducing anticonvulsant
E_{max}	Maximum effect
FACTS	Fixed and Adaptive Clinical Trial Simulator
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FSH	Follicle Stimulating Hormone
FTIH	First time in human
g	Gram(s)
GCP	Good clinical practice
GI	Gastrointestinal
gIC50	growth half maximal inhibitory concentration
GLP	Good laboratory practices
GSK	GlaxoSmithKline
HbsAg	Hepatitis B surface antigen
HCTZ	Hydrochlorothiazide
HDL	High-density lipoprotein
hERG	Human *ether-à-go-go*-related gene
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
HNSTD	Highest non-severely toxic dose
hr	Hour(s)
HRT	Hormone replacement therapy
IB	Investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent ethics committee/institutional review board
IL-6	Interleukin 6
IL-8	Interleukin 8
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IUS	intrauterine system
IV	Intravenous
IVCD	Intraventricular conductance delay

kg	Kilogram(s)
l	Liter(s)
LDL	Low-density lipoprotein
LHRH	Luteinizing hormone releasing hormone
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LPS	Lipopolysaccharide
LVEF	Left ventricular ejection fraction
m^2	Meters squared
MABEL	Minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MI	Myocardial infarction
min	Minute(s)
MIP1-α	Macrophage inflammatory protein 1 alpha
mIU	Milli International Units
ml	Milliliter(s)
μM	Micromolar
mm^3	Cubic millimeters
MM	Multiple myeloma
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSDS	Material safety data sheet
msec	Millisecond(s)
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
N-CRM	Neuenschwander - Continuous Reassessment Method
ng	Nanogram(s)
NMC	NUT midline carcinoma
NOAEL	No observed adverse effect level
NOD/SCID	Non-obese diabetic/severe combined immunodeficiency
NSCLC	Non-small cell lung cancer
NT-proBNP	N-terminal pro–B-Type natriuretic peptide
NUT	Nuclear protein in testes
NYHA	New York Heart Association
OAT3	organic anion transporter 3
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression-free survival
pg	Picogram(s)
PgP	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetic

pmol	Picomole(s)
PR	Partial response
PSA	Prostate specific antigen
PSA50	50% decrement in baseline PSA
PT	Prothrombin time
p-TEFB	Positive transcription elongation factor complex
PTS	Platform Technology & Science
PTT	Partial thromboplastin time
QTc	Corrected QT interval
QTcF	Corrected QT (Fridericia's formula)
RAP	Reporting and Analysis Plan
RECIST	Response criteria in solid tumors
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
Ro	The observed accumulation ratio
RP2D	Recommended Phase 2 dose
SAE(s)	Serious adverse event(s)
SAS	Statistical Analysis System
SCLC	Small cell lung cancer
SD	Standard deviation
SPM	Study Procedure Manual
SRT	Safety review team
STD10	Severely toxic dose in 10% of the animals
$t_{½}$	Half-life
TID	Three times daily
t_{max}	Time to C_{max}
TSH	Thyroid Stimulating Hormone
TSS	Transcription start site
TTE	Transthoracic echocardiogram
ULN	Upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
CredibleMeds
FACTS
SAS
WinNonlin

14.2. Appendix 2: ECOG Performance Status

The performance status assessment is based on the ECOG scale [Oken, 1982]

0 = Fully active, able to carry on all pre-disease performance without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 = Dead.

14.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject <u>with</u> entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥ 5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 4) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, aspartate aminotransferase [AST], alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • Blood sample for pharmacokinetic (PK) analysis, obtained 2 days after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA,et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos*. 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P,et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol*. 2005;43(5):2363–2369.

14.4. Appendix 4: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [**Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 9.

2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 9.

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS,et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

14.5. Appendix 5: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and response to medicine, including GSK2820151 or any concomitant medicines.

US Food and Drug Administration states that an *in vitro* companion diagnostic device (IVD) could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from a particular therapeutic product;
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product;
- Monitor response to treatment for the purpose of adjusting treatment (e.g. schedule, dose, discontinuation) to achieve improved safety or effectiveness

Global regulatory requirements for IVD companion diagnostic tests are evolving. If a DNA-based IVD companion diagnostic device might be needed to identify patients who are appropriate for the GSK medicinal product(s) under investigation in this protocol, then GSK should collect and retain DNA samples from subjects who carry the genetic variant of interest as well as DNA samples from subjects who do not carry the genetic variants of interest to validate the performance of the companion diagnostic. Any IVD companion diagnostic research objectives should be described in subject informed consent forms.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in the RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

14.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

14.6.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

14.6.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Refer to Appendix 2 for the required liver chemistry follow-up instructions

14.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

14.6.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

14.6.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

14.6.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and e-mail it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

14.7. Appendix 7: Guidelines for Management of Toxicity

The following dose modification criteria should provide guidance for, but not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that drug. Dose modifications should be made after discussion with the GSK medical monitor.

14.7.1. Dose Adjustments for Toxicity

Table 12 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	• Continue current dose of GSK2820151 • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4mol/L (2) Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	• Discontinue GSK2820151 and notify the GSK Medical Monitor. (1) Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L (2) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (3) Discontinue any concomitant medications with potential for QTcF prolongation. (4) Consider telemetry monitoring if clinically indicated. • This subject may consider restarting study treatment at a previous dose level if the following criteria for QTcF rechallenge are met: • QTcF Rechallenge Procedures: Do not rechallenge with study treatment unless under the following conditions: (1) QTcF event reduced to <450 msec, (2) potassium and magnesium levels are within institutional normal range, (3) a favorable risk/benefit profile (in the medical judgement of the Investigator and the GSK Medical Monitor),

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		(4) approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. • If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be monitored weekly for two weeks, and then next assessment at 4 weeks post-dose. If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN	• Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin within 24-48 hours or as soon as possible. • If the subject is asymptomatic and repeat value is within the normal range, the subject may continue GSK2820151 with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. • If the repeat value remains > ULN AND the subject is asymptomatic, hold GSK2820151, refer to a cardiologist, and contact the GSK Medical Monitor. May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor. • If the subject is symptomatic (symptoms consistent with acute coronary syndrome) OR the troponin level is at or above the threshold for mycocardial infarction (MI) according to local lab parameters, discontinue GSK2820151 permanently and refer the subject immediately to a cardiologist or emergency medical facility for appropriate medical care.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
LVEF	Ejection fraction below the institution's lower limit of normal (LLN) <u>AND</u> An asymptomatic, absolute decrease of >10% in LVEF compared to baseline	Withhold GSK2820151 and repeat evaluation of LVEF within 2 weeks If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution, whichever is longer.
	Grade 3 or 4	Permanently discontinue GSK2820151. Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution, whichever is longer.
Liver		Refer to procedures outlined in Appendix 3: Liver Safety Required Actions and Follow up Assessments
Hypo- and Hyperglycemia Note: for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE version v4.03 Grade 1-5	Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)	• Monitor fasting and preprandial glucose. • If persistent over 2 repeats over 3-4 weeks, consult Diabetologist and consider starting metformin

	Any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)	• Withhold GSK2820151 and instruct subject to notify investigator immediately.
		  • Monitor for ketoacidosis as clinically indicated.
		  • If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist . Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve.
		• May consider restarting GSK2820151 at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	Withhold GSK2820151 Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes, may restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.
Diarrhea	Grade 1	• Initiate supportive care including loperamide.
	Grade 2	• Initiate supportive care including loperamide. • Consider temporary discontinuation of GSK2820151 and discuss with GSK Medical Monitor.
	Grade 3	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Withhold GSK2820151 until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxisIf diarrhea recovers to ≤ Grade 1 , discuss with medical monitor; consider resuming treatment at the same or lower dose based on clinical judgement.
	Grade 4	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Discontinue GSK2820151 permanently
Mucositis	Grade 1 or 2	• Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
	Grade 3 or 4	• Above, plus systemic opiate administration as needed. • Consider IV hydration and hospital admission as appropriate. • For mucositis ≥ Grade 3, withhold GSK2820151 until mucositis is ≤ Grade 1 and resume the same dose of GSK2820151. If mucositis ≥ Grade 3 recurs, withhold GSK2820151 until mucositis is ≤ Grade 1, then reduce GSK2820151 one dose level. If mucositis ≥ Grade 3 recurs a third time at reduced dose, discontinue GSK2820151 permanently. •
Pneumonitis	Grade 1	• Consider evaluation by pulmonologist. • Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). If any decline is observed in O_2 saturation,

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		withhold study drug, repeat chest x-ray to determine if progression of pneumonitis has occurred and consult pulmonologist. • Obtain high-resolution computed tomography (CT) scan of the chest if possible.
	Grade 2	• , then reduce dose by at least 25%. • Must be evaluated by pulmonologist. • Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to baseline. • Obtain high-resolution chest CT if possible. • Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL). • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated. • Withhold GSK2820151 until recovery to ≤ Grade 1, then reduce dose by at least 25%. Discontinue GSK2820151 if no recovery to ≤Grade 1 within 4 weeks.
	Grade 3 or 4	• Discontinue GSK2820151 and refer for evaluation by pulmonologist • Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to baseline. • Obtain high-resolution chest CT if possible. • Bronchoscopy with biopsy and/or BAL is recommended. • Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. • Rechallenge Guidelines • Grade 3: Withhold GSK2820151 until recovery to < Grade 1. Discontinue GSK2820151 if no recovery to < Grade 1 within 4 weeks. May consider restarting GSK2820151 at a reduced dose after discussion with GSK Medical Monitor if there is clinical benefit. • Grade 4: Rechallenge with GSK2820151 is not permitted

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Fever	Grade 1	• Continue current dose of GSK2820151 and monitor for change in severity.

	Grade 2	• Temporarily discontinue GSK2820151 and monitor for change in severity.
		  • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. Assess vital signs.
		  • Collect cytokine blood samples as outlined in the Laboratory Manual. Collect blood culture and investigate viral infections as applicable
		• Consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.

	Grade 3 or 4	• Temporarily discontinue study medication and monitor for change in severity.
		  • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea.
		  • Collect cytokine blood samples as outlined in the Laboratory Manual. Collect blood culture and investigate viral infections as applicable.
		• Consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor

Thrombocytopenia	Grade 1 (platelets <LLN to ≥75,000/mm^3) or Grade 2 (platelets <75,000 to ≥50,000/mm^3)	• Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000 to ≥25,000/mm^3)	• Withhold GSK2820151 and check aPTT, PT, and INR. Monitor CBC and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Withhold GSK2820151 until thrombocytopenia has resolved to ≤ Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued permanently or restarted at further lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur to the same level following a second rechallenge, drug

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		will be discontinued permanently.
	Grade 4 (platelets≤ 25,000) or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK2820151 and check aPTT, PT, and INR. Monitor CBC and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Withhold GSK2820151 until thrombocytopenia has resolved to ≤ Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued permanently. If platelet count does not recover to ≥25,000/mm^3 (Grade 3) within 7 days and ≥50,000/mm^3 (Grade 2) within 14 days, GSK2820151 should be permanently discontinued. Any subject requiring transfusion support, GSK2820151 should be permanently discontinued. •
All Other Toxicity*	1	• Continue dosing with no change
	2	• Continue dosing with no change OR • Withhold GSK2820151 for up to 1 week for toxicity to be < Grade 2, then continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	3	• 1st episode: Withhold dose for one week intervals until ≤ drug-related Grade 2, then restart with no change. • 2nd episode: Utilize an alternative, less frequent schedule or reduce by one dose level. • If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.
	4	• Discontinue GSK2820151 • In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the subject is receiving benefit then the episode may be managed as per Grade 3 toxicity.

*Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for certain AEs as defined in Section 4.2.5.

14.8. Appendix 8: Guidelines for Assessment of Disease, Disease Progression, and Response Criteria – adapted from RECIST 1.1 [Eisenhauer, 2009]

14.8.1. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules) [Eisenhauer, 2009].

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

14.8.2. Guidelines for Evaluation of Disease

14.8.2.1. Measurable and Non-measurable Definitions

14.8.2.1.1. Measurable lesion

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥ 20 mm).
- ≥ 10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥ 20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

14.8.2.1.2. Non-measurable lesion

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

14.8.3. Baseline Documentation of Target and Non-Target Lesions

- All baseline lesion assessments must be performed within [28] days of randomization.

- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

14.8.4. Response Criteria

14.8.4.1. Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.

- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

14.8.4.2. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in

target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

14.8.4.3. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

14.8.4.4. Evaluation of overall response

Table 13 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 13 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Table 14 presents the overall response at an individual time point for all possible combinations of tumor responses in non-target lesions with or without the appearance of new lesions for subjects with non-measurable only disease at baseline.

Table 14 Evaluation of Overall Response for Subjects with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=Not Evaluable		

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.8.4.5. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 49 days (based on the expected 56 ± 7 day window)
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

14.8.4.6. Confirmation Criteria

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

Reference

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). Europena Journal of Cancer. 2009; 45: 228-247.

14.9. Appendix 9: Cockcroft and Gault Method for Calculated Creatinine Clearance

Calculated creatinine clearance (mL/min) =	(140 – age [yrs]) × weight (kg)
	72 × serum creatinine (mg/100mL)
Female patients: multiply by 0.85	

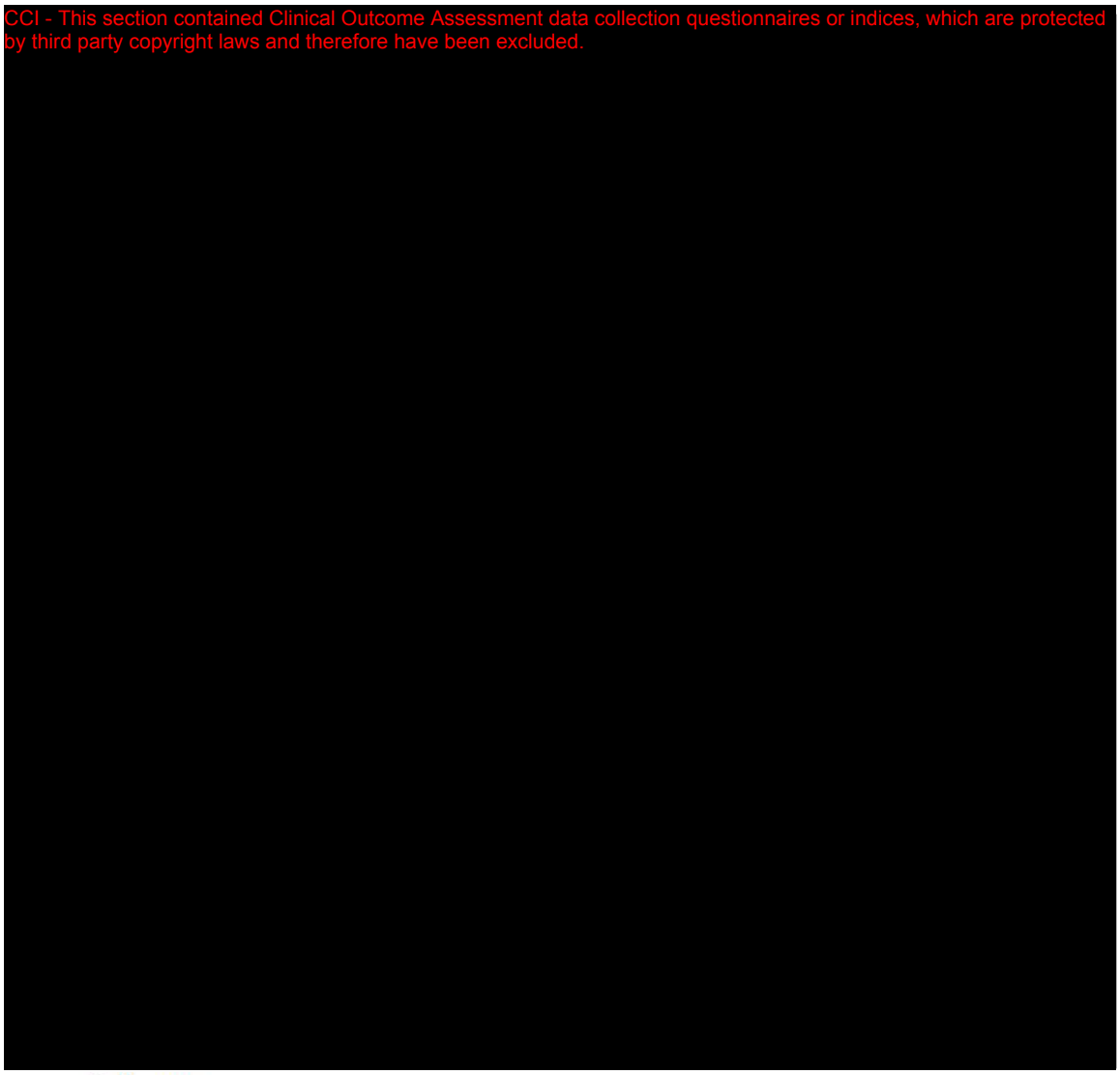
[Cockcroft, 1976]

14.10. Appendix 10: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- **Any female subject who becomes pregnant while participating:**
    - will discontinue study medication
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

14.11. Appendix 11: Pain Assessment (Wong-Baker Faces Pain Rating scale)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



Reference

Wong, D. and Whaley, L. (1986). Clinical handbook of pediatric nursing, ed., 2, p. 373. St. Louis: C.V. Mosby Company.

14.12. Appendix 12: NYHA Functional Classification System for Heart Failure

The New York Heart Association (NYHA) Functional Classification [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of four categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

14.13. Appendix 13: Protocol Amendment Changes

Amendment 1 (19-JUN-2015) from the Original Protocol (15-Dec-2014)

Where the Amendment Applies

Amendment 1 applies to all study centres.

General Protocol Changes
Amendment 1 includes, change in the Primary Medical Monitor, the clarification of Dose Escalation Schedules (Section 4.2) to make it clearer. Minor corrections in the summary of gastrointestinal risk. In light of emerging data from preclinical studies of embryo-fetal development, reproductive risk section, inclusion criterion #9 and guidance on contraception use were updated. List of prohibited and permitted medicines has been revised. Added more clarity on study termination criteria and greater flexibility on W3D4 PK samples window period. Statement on pregnancy follow-up inserted. Reference list updated.

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

List of Changes

TITLE PAGE

Authors:

Rationale for change: Additional author contributed to the amendment added and authors not involved in the study deleted.

Revised Text:

Addition of Author:

PPD

Deletion of Authors:

PPD

Medical monitor/Sponsor Information Page

Medical Monitor/SAE Contact Information:

Rationale for change: Primary medical monitor has changed.

Revised Text:

Role	Name	Day Time Phone Number and email address	After Hours Contact Information	Site Address
Primary Medical Monitor	PPD ~~MD/PhD~~ PPD MB, FFPM	PPD		GlaxoSmithKline ~~1250 South Collegeville~~ Gunnels Wood Road, ~~UP4210 Collegeville, PA 19426, USA~~Stevenage Hertfordshire SG1 2NY, UK

Section 4.2. Dose Escalation and Duration of Study

Rationale for change: The change was made to give more clarity in the dose escalation schedules.

Revised Text:

First Paragraph:

This study will utilize an accelerated dose escalation phase in order to minimize sub-optimal drug exposures, followed by a conventional 3+3 dose escalation phase to achieve MTD. ~~At least one and up to six subjects will be recruited per cohort.~~ Initially, one subject per dose cohort will be recruited (accelerated dose escalation phase) until the first instance of a ≥ Grade 2 drug related non-hematological toxicity. Further cohorts will be recruited in blocks of three subjects (3+3 dose escalation phase). Additional subjects may be enrolled at previously cleared dose levels in order to obtain further data for PK and/or PD analysis. ~~A maximum of six subjects will be assigned to any single dose.~~ *Once MTD is determined,* ~~up to 12~~ additional subjects (18 subjects total at MTD) may be enrolled to collect additional safety data (Figure 2). The total duration of study for each subject will be dependent upon the safety, tolerability and efficacy of GSK2820151.

4.2.2. Accelerated Dose Escalation

Rationale for change: The change was made to give more clarity in the dose escalation schedules.

Revised Text:

Third Paragraph:

At the first occurrence of a DLT (refer to Section 4.2.4) or any Grade 2 toxicity ~~(~~based on NCI-CTCAE v4.03~~)~~ (with the exception of Grade 2 alopecia, nausea, vomiting, diarrhea, hemoglobin, lymphopenia, taste changes or alkaline phosphatase in the presence of bony

metastases) during the first 4 weeks, the Accelerated Dose Titration ~~procedure~~ phase will be terminated~~. Once a DLT occurs,~~ and the ongoing cohort will be expanded up to 6 subjects ~~and dose-escalation will continue following~~ to commence the 3 + 3 Dose-Escalation ~~guidelines~~ phase of the study.

Section 4.2.3. 3 + 3 Dose Escalation

Rationale for change: The change was made to give more clarity in the dose escalation schedules.

Revised Text:

If the accelerated dose titration ends due to > grade 2 toxicity then t~~T~~wo additional subjects will be enrolled to ~~the~~ same dose level ~~at which accelerated dose titration ends, for a total of at least 3 subjects at that dose level.~~ where as, if termination of accelerated dose titration is due to DLT, then up to 5 additional subjects will be enrolled at the same dose level to continue the treatment following the 3 + 3 Dose Escalation guidelines~~. If no DLTs are observed in any of the 3 subjects, then dosing will proceed to the next higher dose level (≤2 fold increase in dose); however, if termination of accelerated dose titration is triggered by a DLT, then 5 additional subjects will be enrolled at that dose level.~~ Subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the MTD in multiple subjects. Dose escalation decisions will be made as outlined in Table 2 Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. Intra-subject dose escalation may be considered as described in Section 4.2.7. Subjects should not be enrolled at a higher dose level until at least 3 subjects in the previous dose cohort complete 4 weeks of treatment.

Section 4.6.1. Risk Assessment

Rationale for change: To add clarity in summary data/rational for Risk for Gastrointestinal and Reproductive as potential risk of clinical significance. Also to add mitigation strategy for Reproductive.

Revised Text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal (GI) (Dose-limiting toxicity in rats and dogs)	Gastrointestinal effects were the dose limiting toxicity~~in both~~, observed following repeat dosing in rats and dogs at ~~doses ≥6~~ ≥3 and ~~20~~≥10 mg/kg/day respectively. ~~Clinical presentation included altered feces, reduced food consumption and reduction in body weight; microscopic~~	ICF includes the risk of gastrointestinal effects. Protocol includes medical history, physical examination (including weight) and clinical laboratory assessments to assess toxicity in the GI tract. Subjects with a history of gastrointestinal bleeding in the past 6 months (Section 5.2) or active bleeding will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	~~changes observed at doses ≥6 and 20 mg/kg/day in rats and dogs respectively included erosion / ulceration / haemorrhage / mucosal epithelium degeneration/regeneration, villous atrophy, inflammatory cell infiltration and mild cecal lamina propria fibrosis (dogs only).~~ Clinical presentation included altered feces, reduced food consumption and body weight reductions. These changes correlated with microscopic findings throughout the GI tract of rats given ≥6 mg/kg/day and dogs at 20 mg/kg/day. Microscopic findings included erosion/ulceration, mucosal epithelium degeneration/regeneration and inflammatory cell infiltration (rats and dogs) and minimal to mild hemorrhages, villous atrophy and mild cecal lamina propria fibrosis (dogs only). Signs of recovery were observed immediately after cessation of dosing; no abnormal microscopic findings were evident following a ~~after up~~ 3 to 5 week~~s~~ off dose period.	excluded. Protocol also includes specific dose adjustment/stopping safety criteria for diarrhea and mucositis.
Reproductive	Animal reproductive studies have not been conducted with GSK2820151. No ovarian changes were observed in toxicology studies of up to 4 weeks duration; however, an assessment of estrous cycling was not conducted. BRD2, BRD3, BRD4 and BRDT have	ICF includes the risk of damage to reproductive organs such as testes or ovaries including potential risk to embryofetal development. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	crucial roles in reproduction and development [Paillisson, 2007; Trousdale, 2004] and would be expected to adversely affect embryofetal development. A compound with a similar pharmacology profile, has shown detrimental effects on rat female fertility and embryo-fetal development at clinically relevant exposures. This information indicates that GSK2820151 will likely have similar adverse effects on female fertility and embryo-fetal development. Testicular degeneration was observed in both rats (10 mg/kg) and dogs as well as disorganised spermatogenesis in dog at ≥5 mg/kg. Secondary changes were evident in epididymides (hypospermia, degenerate cells, atrophy, vacuolation). No evidence of reversibility within 3 week off dose period. Reversible reduced prostate weight (rat and dog) & decreased secretory content in prostate (rat ≥ 3 mg/kg/day) and seminal vesicles (rat 10 mg/kg/day) were observed.	for female subjects and collecting testosterone (free and complete) for male subjects.<br~~ICF includes the potential risk of reproductive effects.~~ Due to the effects of GSK2820151 on the male reproductive system and potential for GSK2820151 to be present in semen, men should adhere to the contraceptive guidance detailed in the protocol.

Section 5.1. Inclusion Criteria

Rationale for change: The change was made as emerging pre-clinical data favors the long term use of the contraception in female subjects after the last dose of study medication.

Revised Text:

Inclusion criterion 9: A female subject is eligible to participate if she is of:

Bullet point 2: Child-bearing potential and agrees to use one of the contraception methods (described in Section 7.3) for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until at least ~~4 weeks~~ 7 months after the last dose of study medication.

Rationale for change: The reason for this change was because GSK2820151 may be carried in the semen.

Revised Text:

Inclusion criterion 10: Male subjects with female partners of child bearing potential must agree to use one of the methods of contraception specified (see Section 7.4). This method must be used from the time of the first dose of study medication until ~~at least~~ 16 weeks after the last dose of study medication. In addition, male subjects whose partners are or become pregnant on study medication must continue to use condoms for 7 days after stopping study medication.

Section 5.4.5. Other Stopping Criteria

Rationale for change: The change was made to add a criteria for termination of the study by the sponsor**.**

Revised Text:

Fourth paragraph onwards:

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, and/or if deaths related to study drug are observed, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded. The final determination will be made by the Sponsor and investigators.

The sponsor may also terminate the study if the safety, pharmacokinetics (PK) or pharmacodynamic (PD) data suggest that an appropriate therapeutic exposure cannot be achieved using the dosing schedules defined in the protocol.

Section 7.1.2.1. Prohibited Medications

Rationale for change: The change was made to update the list of drug with a risk of Torsades de Pointes that are prohibited based on the 2015 guidelines.

Revised Text:

Table 5 Drugs with a Risk of Torsades de Pointes that are Prohibited

Amiodarone	Dronedarone	Pimozide
Anagrelide	Droperidol	Procainamide
Azithromycin	Erythromycin	Propofol
Chloroquine	Escitalopram	Quinidine
Chlorpromazine	Flecainide	Sevoflurane ~~Quinidine~~
Cilostazol	Fluconazol	Sotalol
Ciprofloxacin	Halofantrine	Thioridazine
Citalopram	Haloperidol	
Clarithromycin	Ibutilide	
Cocaine	Levofloxacin	
Disopyramide	Methadone	
Dofetilide	Moxifloxacin	
Donepezil	Pentamidine	

Data Source: crediblemeds.org revision date ~~26 September 2014~~ 4 May 2015.

Drugs not available/used in the US have been omitted

Section 7.1.3. Cautionary Medications

Rationale for change: The change was made to update the list of drug with a risk of Torsades de Pointes which are permitted for co-administration with extreme caution based on the 2015 guidelines.

Revised Text:

Table 6 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Alfuzosin	Iloperidone	Ranolazine
Apomorphine	Isradipine	Rilpivirine
Aripiprazole	Lithium	Risperidone
Atazanavir	Mifepristone	Saquinavir
Atomoxetine	Mirabegron	Tacrolimus
Bedaquiline	Mirtazapine	Telavancin
Clomipramine	Moexipril/HCTZ	Telithromycin
Clozapine	Nicardipine	Tetrabenazine
Desipramine	Norfloxacin	Tizanidine
Dexmedetomidine	Nortriptyline	Tolterodine
Dihydroartemisinin+piperaquine	Ofloxacin	Toremifene
Dolasetron	Olanzapine	Trimipramine
Famotidine	Ondansetron	Vardenafil
Felbamate	Oxytocin	Venlafaxine

Fingolimod	Paliperidone	Ziprasidone
Foscarnet	Pasireotide	
~~Fosphenytoin~~	Perflutren lipid microspheres	
Gemifloxacin	Promethazine	
Granisetron	Quetiapine	

Data Source: crediblemeds.org revision date ~~26 September 2014~~ 04 May 2015 Note: This list is not exhaustive. Drugs ~~and/or drug names~~ not available/used in the US have been omitted

Section 8.1. Time and Events Tables

Rationale for change: Window period for PK and biomarker samples at W3D4 changed from +2 to +7 days to allow greater flexibility for 2-on-1-off dosing.

Revised Text:

Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

Addition of text in the table header: **W3D4 + 2 days** (+2 to +7 days for alternate dosing schedule)

Section 8.3.10. Pregnancy

Rationale for change: The change was made as emerging pre-clinical data favors the long term use of the contraception in female subjects after the last dose of study medication. Also follow-up details added for recording the safety of the subject.

Revised Text:

- ~~Details of all~~ Reporting of any pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until ~~14 days~~7 months following the last dose of GSK2820151.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Details on ~~and should~~ follow-up ~~the~~ procedures outlined in Appendix 7.

Section 13. REFERENCES

Rationale for change: Data sources were added/updated

Revised Text:

James LP. 2009. Pharmacokinetics of Acetaminophen-Protein Adducts~~...~~ in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Disp, 2009; 37: 1779-1784.

Addition of References:

Paillisson A, Levasseur A, Gouret P, Callebaut I, Bontoux M, Pontarotti P et al. Bromodomain testis-specific protein is expressed in mouse oocyte and evolves faster than its ubiquitously expressed paralogs BRD2, -3, and -4. Genomics, 2007;89: 215-23.

Trousdale RK and Wolgemuth DJ. Bromodomain containing 2 (Brd2) is expressed in distinct patterns during ovarian folliculogenesis independent of FSH or GDF9 action. Molecular Reproduction and Development, 2004;68:261-8.

Amendment 2 (06-OCT-2015) from the Amendment 1 (19-JUN-2015)

Where the Amendment Applies

Amendment 2 applies to all study centres.

General Protocol Changes

Amendment 2 is mainly in response to FDA request and includes: changes in the Medical Monitors; modified the inclusion criteria and other relevant parts of the protocol to allow only patients with histologically or cytologically confirmed solid malignancy that is either metastatic or unresectable; revised hematologic DLT definition for platelets which now also include Grade 3 thrombocytopenia with clinically significant bleeding in addition to Grade 4 thrombocytopenia (platelets <25,000/mm^3); added in the Dose Stopping Safety Criteria to permanently discontinue the patients from GSK2820151 who experience symptomatic (symptoms consistent with acute coronary syndrome) troponin elevation. Also, included an interim analysis for futility and safety review when 20 patients would have been recruited at the RP2D. Added clarification around collection of blood sample for pharmacokinetics (Section 8.4.1)

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

List of Changes

Medical monitor/Sponsor Information Page

Medical Monitor/SAE Contact Information:

Rationale for change: Primary and secondary medical monitor have changed. Updated contact information of both the medical monitors.

Revised Text:

Role	Name	Day Time Phone Number and email address	After Hours Contact Information	Site Address
Primary Medical Monitor	PPD PPD ~~MB, FFPM~~ PPD MD, D.Phil., FRCPath	PPD		~~GlaxoSmithKline Gunnels Wood Road Stevenage Hertfordshire SG1 2NY, UK~~ GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom
Secondary Medical Monitor	PPD ~~MD/PhD~~ PPD MD, MPH			~~GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA~~ ICON Clinical Research LLC 2100 Pennbrook Parkway North Wales, PA United States, 19454

Protocol Synopsis

Type and Number of Subjects

Rationale for change: The change was made in response to the FDA request for further clarifying the type of subjects to be involved in the study.

Revised Text:

First paragraph and first two bullet points:

Approximately 30 to 50 subjects with will be enrolled in the study. The study population will be adults, with advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable, who either:

- refuse standard curative or palliative therapy,
- are not candidates for standard curative or palliative therapy,

Section 4.2.4 Dose-Limiting Toxicity

Rationale for change: The change was made in response to FDA request to incorporate Grade 3 thrombocytopenia with bleeding as DLT.

Revised Text:

Table 3 Dose –Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 for ≥5 days) • Febrile neutropenia (as defined by NCI-CTCAE v4.03 [concurrent Grade 4 neutropenia and fever >38.3°C]) • Grade 4 anemia of any duration • Grade 3 thrombocytopenia with clinically significant bleeding or ~~G~~grade 4 thrombocytopenia (platelets <25,000/mm^3)

Section 4.3. Type and Number of Subjects

Rationale for change: The change was made in response to the FDA request for further clarifying the type of subjects to be involved in the study.

Revised Text:

Second Paragraph and first two bullet points:

Approximately 30 to 50 subjects with refractory, histologically or cytologically confirmed, advanced (metastatic or unresectable) solid malignancies will be enrolled in the study. The study population will be adults, with advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable, who either:

- refuse standard curative or palliative therapy,
- are not candidates for standard curative or palliative therapy,

Section 5.1. Inclusion Criteria

Rationale for change: The change was made in response to the FDA request for further clarifying the inclusion criteria of subjects to be involved in the study.

Revised Text:

Inclusion criterion 3: Diagnosis of advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable. At time of enrollment, subjects either:

Bullet point 1: refuse standard curative or palliative therapy,

Bullet point 2: are not candidates for standard curative or palliative therapy,

Section 5.4. Withdrawal/Stopping Criteria

Rationale for change: The change was made to incorporate the "raised Troponin level" for further clarifying the Withdrawal/Stopping Criteria.

Revised Text:

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry, hematologic/non-hematologic toxicity, QTc prolongation, raised Troponin level as defined in Section 14.7.1 or left ventricular ejection fraction (LVEF)/valvular dysfunction as defined in Section 5.4.1 through Section 5.4.5.

Section 8. Study Assessments and Procedures

Rationale for change: The change was made to correct the typographical error in Table 10 – window period (W9D1)

Revised Text:

Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days (+2 to +7 days for alternate dosing schedule)										**W9D1 ±4 +4 days** (if dose has been escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±4h**	**24h ±1h**	**48h ±1h**	**pre dose**	**0.5-2h**	**4 - 8h**	

Section 8.2.2. Visit Windows

Rationale for change: The change was made to correct the typographical error in window period (Week 2 to Week 4)

Revised Text:

Third Paragraph:

Week 2 to Week 4: Based on subject and clinic schedule, assessments can be ~~+3~~ ±3 days.

Section 8.4.1. Blood Sample Collection for Pharmacokinetics

Rationale for change: The change was made for clarification on blood sampling and analysis for PK

Revised Text:

Second Paragraph:

Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded along with the date and time of the prior dose administration. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. This will not require a protocol amendment. In addition, plasma samples may be analyzed qualitatively for other circulating compound-related material and the results will be reported under a separate Drug Metabolism and Pharmacokinetics (DMPK) protocol.

Section 11.4.2. Interim Analysis

Rationale for change: The change was made in response to the FDA request for inclusion of the Interim analysis for monitoring the safety of subjects.

Revised Text:

Second paragraph:

If this trial enrols more than 20 patients at the recommended phase 2 dose (RP2D), an interim analysis for futility and complete review of safety data will be performed on first 20 patients treated. This analysis will be used to evaluate the risk-benefit of continued treatment of these patients and to assess the risks related to delayed GSK2820151-related toxicities.

Section 14.7. Appendix 7: Guidelines for Management of Toxicity

Rationale for change: The change was made in response to the FDA request to permanently withdraw the subjects who experience symptoms consistent with acute coronary syndrome in addition to raised troponin level.

Revised Text:

Table 12 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines

Troponin	Troponin level >ULN	• Evaluate immediately for symptoms and obtain ECG. Repeat troponin within 24-48 hours or as soon as possible.
		  • If the repeat value is within the normal range, the subject may continue GSK2820151 with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated.
		  • If the repeat value remains > ULN AND the subject is asymptomatic, withhold GSK2820151, refer to a cardiologist, and contact the GSK Medical Monitor. May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.
		  • If the subject is symptomatic (symptoms consistent with acute coronary syndrome) OR the troponin level is at or above ~~approaches~~ the threshold for mycocardial infarction (MI) according to local lab parameters, ~~hold~~ discontinue GSK2820151 permanently and refer the subject immediately to a cardiologist or emergency medical facility for appropriate medical care.
		• ~~May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.~~

Amendment 3 (23-MAY-2016) from the Amendment 2 (06-OCT-2015)

Where the Amendment Applies

Amendment 3 applies to all study centres.

General Protocol Changes
Amendment 3 includes:

- Inclusion criterion # 3 has been amended to allow the subjects who had progressed >3 prior line therapies. Exclusion criterion # 2 has been deleted to lift the restriction of 3 prior lines of cytotoxic therapy.

- MUGA Scan that had been stated as a second optional method for the measurement of ejection fraction has been removed from inclusion criterion #7.

- Clarification was made on the collection time for screening holter monitoring in Section 8.3.7. It was not intended to have holter required at Day-1 but rather performed within the 14 day screening window as outlined in the T/E table. Also, time points for holter monitoring were matched with triplicate ECGs time points. Time & Events Table was updated to reflect the same.

- Minor correction made on AEs and SAEs reporting period in Section 9.2.

- Added more clarity on pain assessment which will be performed using Wong-Baker Faces Pain Rating scale. Appendix 11: Wong-Baker Faces Pain Rating scale added.

- A clarification on the collection and processing of safety cytokines, PK and protein biomarker samples process was made in Time & Events Table.

- No Triplicate ECG on W1D2, Time & Events Table corrected.

- Section 7.1.2.2, typo corrected "Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the **screening** visit through the post-study follow-up visit."

Changes are noted below with ~~strikethrough~~ to identify deleted text and underlining to identify new or replacement text.

List of Changes

Protocol Synopsis

Type and Number of Subjects

Rationale for change: Limiting the prior number of therapies to 3 was posing restrictions on patients screening so removed to allow more flexibility. There was discrepant information within the 201893 Protocol Amendment 2, regarding the time

points for the holter monitoring which should be in line with triplicate ECG time points; so corrections were made.

Revised Text:

First paragraph, fourth bullet point:

Approximately 30 to 50 subjects with will be enrolled in the study. The study population will be adults, with advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable, who either:

- refuse standard curative or palliative therapy,
- are not candidates for standard curative or palliative therapy,
- have a disease for which no non-investigational therapy exists, OR
- have progressed on prior therapy ~~(up to three lines of prior cytotoxic agents are permitted)~~ (radiographic documentation of progression is adequate for study participation).

The total number of subjects required will depend upon the number of escalation steps required to reach a MTD.

Analysis

Measurements

- **SAFETY MEASUREMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events will be performed. Stringent cardiac safety monitoring will be required, consisting of:
  - ≥ 48 hours of telemetry following the first dose (necessitating overnight stays in a research facility)
  - 24 hours of ambulatory cardiac (Holter) monitoring in Week 1, Week 2, Week 34, and Week 9

Section 4.3. Type and Number of Subjects

Rationale for change: Limiting the prior number of therapies to 3 was posing restrictions on patients screening so removed to allow more flexibility.

Revised Text:

Second paragraph, fourth bullet point:

Approximately 30 to 50 subjects with refractory, histologically or cytologically confirmed, advanced (metastatic or unresectable) solid malignancies will be enrolled in the study. The study population will be adults, with advanced or recurrent, histologically

or cytologically confirmed, solid malignancy that is either metastatic or unresectable, who either:

- refuse standard curative or palliative therapy,
- are not candidates for standard curative or palliative therapy,
- have a disease for which no non-investigational therapy exists, OR
- have progressed on prior therapy ~~therapy (up to three lines of prior cytotoxic agents are permitted)~~ (radiographic documentation of progression is adequate for study participation).

Section 5.1. Inclusion Criteria

Rationale for change: Limiting the prior number of therapies to 3 was posing restrictions on patients screening so removed to allow more flexibility.

Revised Text:

Inclusion criterion #3, fourth bullet point:

3. Diagnosis of advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable. At time of enrollment, subjects either:
   - refuse standard curative or palliative therapy,
   - are not candidates for standard curative or palliative therapy,
   - have a disease for which no non-investigational therapy exists, OR
   - have progressed on prior therapy ~~(up to three lines of prior cytotoxic agents are permitted)~~ (radiographic documentation of progression is adequate for study participation).

Rationale for change: The optional use of the MUGA scan was not included in the inclusion criteria of the synopsis, and sites are advised to use Echocardiogram only

Revised Text:

Inclusion criterion #7, Table 4:

Cardiac	
Ejection fraction	≥ 50% by echocardiogram ~~or multigated acquisition scan (MUGA)~~

Section 5.2. Exclusion Criteria

Rationale for change: Limiting the prior number of therapies to 3 was posing restrictions on patients screening so removed to allow more flexibility.

Revised Text:

Exclusion criterion #2 deleted::

~~2. More than three prior lines of cytotoxic therapy.~~

Section 7.1.2.2. Prohibited Non-Drug Therapies

Rationale for change: Minor correction has been made.

Revised Text:

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the ~~transition~~ screening visit through the post-study follow-up visit.

8.1. Time and Events Tables

Rationale for change: There was discrepant information within the 201893 Protocol Amendment 2, regarding the time points for the holter monitoring which should be in line with triplicate ECG time points; so corrections were made. In previous versions (including Protocol Amendment 2), only pain assessment was mentioned in the protocol. The information that Wong Baker Validated Scale will be used for pain assessment has been added as an additional information. A clarification on the collection and processing of safety cytokines, PK and protein biomarker samples has been added.

Revised Text:

Table 7 Time and Events

Under "Assessments"Column:

Pain (using Wong-Baker Faces Pain Rating scale)

Under "Cardiac Monitoring" Row:

12-lead ECG on Week 1, D2 changed from ~~O~~ to X

Holter monitoring has been added on Week 2, D4 and Week 3, D4 (indicated as X) and deleted on Week 2, D5 and Week 4, D1 (indicated as ~~X~~).

Table 8 Time and Events: Laboratory Assessments

Under Notes column for Safety Cytokines:

This is collected as part of the Predose PK sample and is sent to ~~GSK DMPK~~ Myriad via Covance.

Table 9 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

Footnotes:

Plasma samples will be divided at the site into two, one sample will be shipped to GSK DMPK facility where bioanalysis of PK is performed and the second sample will be sent ~~shipped~~ via Covance to ~~a vendor~~ Myriad for systemic cytokine assessment ~~(pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr)~~ and acute phase protein assessment ~~at pre-dose and at 2,4, 8 and 24 hr post-dose~~. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

Footnotes:

Plasma samples will be divided at the site into two, one sample will be shipped to GSK DMPK facility where bioanalysis of PK is performed and the second sample will be sent ~~shipped~~ via Covance to ~~a vendor~~ Myriad for systemic cytokine assessment and acute phase protein assessment ~~at pre-dose and at 2, 4, 8 and 24 hr post-dose~~. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

Section 8.3.3. Vital Signs

Rationale for change: The pain assessment method information has been added as an additional information.

Revised Text:

Last paragraph:

Pain will be assessed using Wong-Baker Faces Pain Rating scale (Appendix 11).

Section 8.3.7. Holter Monitoring

Rationale for change: There was discrepant information within the 201893 Protocol Amendment 2, regarding the time points for the holter monitoring which should be in line with triplicate ECG time points; so corrections were made.

Revised Text:

Fifth paragraph:

~~Baseline~~ QT/QTcF values will be determined ~~on Study Day -1~~ using time matched ECGs obtained from the Holter monitor ~~at approximately the same~~ on following time points ~~as planned for~~: screening, Week 1 Day 1~~ to 2~~; Week ~~2~~1 Day ~~3 to 4~~ 5, Week ~~3~~ 2 Day ~~5 to 6~~ 4 and Week 4 3 Day ~~7 to~~ 4 and Week ~~5~~9 Day 1. The mean from triplicate ECGs will be evaluated at each time point. For a given time point, the mean QTcF from 3 separate beats should be analyzed on each ECG. Analysis of Lead II will be conducted with V5 as back-up and one of the remaining precordial leads as an alternative when T waves are not

well defined in Leads II or V5. QTcF for an individual beat will be calculated from the preceding RR interval since using the average heart rate (RR) intervals from the ECG could result in inaccurate QTcF calculations due to beat to beat variations in the RR intervals.

Section 8.3.8. Clinical Safety Laboratory Assessments

Rationale for change: Minor correction has been made.

Revised Text:

The abbreviated term ~~SRM~~ *has been replaced by* Laboratory Manual *throughout the section.*

Section 8.4.1. Blood Sample Collection for Pharmacokinetics

Rationale for change: Minor correction has been made.

Revised Text:

Third paragraph:

Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the ~~SRM~~ Laboratory Manual.

Section 8.4.2. Urine Sample Collection for Pharmacokinetics

Rationale for change: Minor correction has been made.

Revised Text:

Third paragraph:

Details of urine sample collection, processing, storage, and shipping procedures are provided in the ~~SRM~~ Laboratory Manual.

Section 9.2. Time period and Frequency for collecting AE and SAE information

Rationale for change: Minor correction has been made.

Revised Text:

First bullet point:

- At each visit/contact, AEs and SAEs will be collected from the first dose (start of Study Treatment) until 28 days after the last dose of study treatment or until the start of new anti-cancer therapy-whichever occurs first. ~~the follow-up contact (see Section 9.2.2), at the timepoints specified in the Time and Events Table (Section 8.1).~~

Section 14.1. Appendix 1: Abbreviations and Trademarks

Rationale for change: Deleted the abbreviation which is not used in the document.

Revised Text:

Deleted text:

~~MUGA~~	~~Multigated acquisition scan~~

Section 14.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

Rationale for change: Minor correction has been made.

Revised Text:

Table footnote #6:

6. ~~PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.)~~ Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the ~~SRM~~ Laboratory Manual.

Section 14.7.1. Dose Adjustments for Toxicity

Rationale for change: Minor correction has been made.

Revised Text:

Table 12 Dose Adjustment/Stopping Safety Criteria

The abbreviated term ~~SRM~~ *has been replaced by* Laboratory Manual *throughout the Table.*

Section 14.11. Appendix 11: Pain Assessment (Wong-Baker Faces Pain Rating scale)

Rationale for change: The pain assessment method information has been added as an additional information.

Revised Text:

A new section/appendix has been added:

Amendment 4 (DD-MMM-YYYY) from the Amendment 3 (23-MAY-2016)

Where the Amendment Applies

Amendment 4 applies to all study centres.

General Protocol Changes

Updates were made throughout the protocol to correct minor inconsistencies, spelling errors and provide further clarification.

The most salient changes in Amendment 4 include:

- GSK Medical Monitor change
- Section 4.6.1 Risk Assessment to include current available data
- Section 5.1 Inclusion Criteria: update to contraception use in Inclusion 9 and 10
- Changes made in Exclusion Criteria Section 5.2
  - clarification made on prior therapy (exclusion criterion-2) and anticoagulation use (exclusion criterion-3)
  - added to exclusion criterion-4 restricted use of NSAIDs and aspirin
  - updated exclusion criterion-13 to include history of bleeding and added known bleeding disorders
- update to Section 7.1 Prohibited Medication and Non-Drug Therapies:
- guidance on the use of exclusionary medications
- prohibited & cautionary medication tables updated
- Contraception requirements updated in Section 7.3 Lifestyle Restrictions
- Corrections made in Time & Events Table 8.1
  - addition of triplicate ECG on W1D2
  - clarification around Pulmonary Function Tests
- Correction made in Table 8 Time and Events: Laboratory Assessments
  - addition of Factor VII assay testing
- Added more clarity to troponin sample collection (Section 8.3.10 Troponin Measurement) and urine PK sample collection (Section 8.4.2 Urine Sample Collection for Pharmacokinetics)
- Appendix 7: dose adjustment/stopping safety criteria updated for QTcF, troponin, LVEF, hypo & hyperglycemia, diarrhea, mucositis, pneumonitis and thrombocytopenia toxicities.
- Appendix 12: NYHA Functional Classification System for Heart Failure Added

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text

List of Specific Changes

Medical monitor/Sponsor Information Page

Medical Monitor/SAE Contact Information:

Rationale for change: Previous Medical Monitor left the company

Revised Text:

Role	Name	Day Time Phone Number and email address	After Hours Contact Information	Site Address
Primary Medical Monitor	PPD ~~MD, D.Phil., FRCPath~~ PPD	PPD		GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom
	MBBS, MBA, MSc			

Section 4.2. Dose Escalation and Duration of Study

Rationale for change: The change was made to give more clarity in the dose escalation criterion.

Revised Text:

First paragraph

This study will utilize an accelerated dose escalation phase in order to minimize sub-optimal drug exposures, followed by a conventional 3+3 dose escalation phase to achieve MTD. Initially, one subject per dose cohort will be recruited *(accelerated dose escalation phase)* until the first instance of a ≥Grade 2 drug related non-hematological toxicity or dose-limiting toxicity (DLT, see Section 4.2.4). Further cohorts will be recruited in blocks of three subjects *(3+3 dose escalation phase).* Additional subjects may be enrolled at previously cleared dose levels in order to obtain further data for PK and/or PD analysis. *Once MTD is determined, additional subjects (18 subjects total at MTD) may be enrolled to collect additional safety data (*Figure 2*). The total duration of study for each subject will be dependent upon the safety, tolerability and efficacy of GSK2820151.*

Second paragraph

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on ~~all available data, including~~ PK data, ~~and~~ the safety profile of the current and prior cohorts, as well as the predicted ~~optimal dose~~ dose-limiting toxicity

(DLT) rates on all potential doses from the Neuenschwander,2008Continual Reassessment Method (N-CRM) analysis [Neuenschwander, 2009],.N-CRM design is a type of Bayesian adaptive dose-escalation scheme (see Section 11.2). The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The DLT information of all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

Section 4.2.2 Accelerated Dose Escalation

Rationale for change: The change was made to give more clarity in the dose escalation criterion.

Revised Text:

First paragraph

One subject per dose level in the accelerated dose escalation phase will be treated to minimize suboptimal drug exposures, starting with Dose Level 1 and will continueing until one subject experiences ≥Grade 2 drug related toxicity (based on National Cancer Institute- Common Terminology Criteria for Adverse Events, Version 4 (NCI-CTCAE v4.03 [NCI-CTCAE, 2010]) or dose-limiting toxicity (DLT, see Section 4.2.4). The accelerated dose titration scheme is described in Table 1. A single dose (Day 1) will be given to subjects in each cohort with the collection of blood samples for PK analysis at timed intervals. Once the final PK sample for Day 1 is obtained, subjects may begin repeat dosing on Day 3. The dose for Dose Level 2 and subsequent cohorts will be based on the pharmacokinetics (PK) and safety analysis of the previous cohort. Inter-subject variability in exposure and toxicity will also be considered when deciding on actual doses administered during dose-escalation. Dose escalation will occur according to the procedures outlined in Table 1.

Section 4.3. Type and Number of Subjects

Rationale for change: The change was made for clarifying the type of subjects to be involved in the study.

Revised Text:

Second paragraph

Bullet point 1: refuse or are not candidates for standard curative or palliative therapy,

Bullet point 2: are not candidates for standard curative or palliative therapy,

Bullet point 3: have a disease for which no non-investigational therapy exists, OR

Section 4.6.1. Risk Assessment

Rationale for change: Updates in Risk assessment table with information from recent studies

Revised Text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiovascular Effects	**QT Prolongation** QT prolongation was ~~O~~observed in dogs after single dosinge ~~in dogs~~ (≥ 10~~0~~ mg/kg; up to 34 milliseconds [msec] and up to 48 hr post dosing) and after repeat dosing ~~in dogs~~ (≥30 mg/kg/day from Day 3; up to 21 msec). ~~Mechanism is unclear (no clear link to~~ A direct effect on human *ether-à-go-go*-related gene [hERG] binding is unlikely.~~)~~; ~~QT prolongation observed at unbound *in vivo* drug concentrations approximately 100-fold lower than in vitro hERG inhibition (IC_{50}).~~Mechanism and risk for Torsades de Pointes is unclear. Increased number of non-fatal arrhythmias were observed in 1 of ~~3~~ 4 dogs which had highest drug exposure after a single dose of 100mg/kg (10x the dog 28 day maximum tolerated dose, or MTD). **Blood Pressure (BP)** Increases in blood pressure (mean, systolic &	Informed consent form (ICF) includes the risk of (fatal) arrhythmias and the risk of myocardial infarction Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 7.1.2). Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK], creatine kinase-MB isoenzyme [CK-MB], and troponins [local laboratory monitoring for troponin I or T based on availability and troponin T at central laboratory]), cardiac monitoring (ECGs, Holter monitoring and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management of cardiac events (refer to Section 14.7.1). All subjects will receive their first dose of study medication (Week 1 Day 1) in the hospital with telemetry monitoring for the first 48 hours of dosing. Throughout the protocol, the role of intensive cardiac monitoring will be re-evaluated in an ongoing fashion with the aim of re-evaluating cardiac risk mitigation

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	diastolic; systolic affected more than diastolic) were observed ~~following single dose~~ in dogs after single dosing ≥10 mg/kg. ~~M~~ (mean up to 38 millimeters mercury [mmHg] and up to 42 hours post dosing). **Heart Rate** Increased heart rate was observed after ~~a~~ single dosing ~~and repeat doses of~~ (100 mg/kg~~; in dogs (single dog~~ up to 24 beats per minute ~~([~~BPM]~~)~~ between 9 and 19 hours post dosing) and in one dog after repeat dosing ~~a single dose and single dog~~ (100 mg/kg; up to ~~94~~64 ~~bpm~~ BPM post dosing)~~after repeat dosing.)~~. **Cardiac Biomarkers** Reversible increases in serum cardiac troponin I (cTnI) levels were observed in male rats (up to 3.3X) at 10 mg/kg/day for 28 days. Increased NT pro-ANP (up to 2.1X) in female rats given ≥1 mg/kg/day for 28 days; no recovery after up to 5 weeks off dose period. No histologic lesions were observed in the heart on 28 day studies.	strategy while maintaining subject safety.
Gastrointestinal (GI) Effects ~~Dose-limiting toxicity in rats and dogs)~~	Gastrointestinal effects were the dose limiting toxicity (DLT)~~,~~ observed following repeat dosing in rats (≥3 mg/kg/day) and dogs ~~at ≥3 and~~ (≥10 mg/kg/day~~) respectively.~~	ICF includes the risk of gastrointestinal effects. Protocol includes medical history, physical examination (including weight) and clinical laboratory assessments to assess toxicity in the GI tract. Subjects with a history of gastrointestinal bleeding in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical presentation included altered feces, reduced food consumption and body weight reductions. These changes correlated with microscopic findings throughout the GI tract of rats given ≥6 mg/kg/day and dogs at 20 mg/kg/day. Microscopic findings in rats and dogs included erosion/ulceration, mucosal epithelium degeneration/regeneration and inflammatory cell infiltration. ~~(rats and dogs) and~~ Microscopic findings in dogs only included minimal to mild hemorrhages, villous atrophy and mild cecal lamina propria fibrosis ~~(dogs only)~~. Signs of recovery were observed immediately after cessation of dosing; no abnormal microscopic findings were evident following a 3 to 5 week off dose period.	the past 6 months (Section 5.2) or active bleeding will be excluded. Protocol also includes specific dose adjustment/stopping safety criteria for diarrhea and mucositis (refer to Section 14.7.1).
Lymphoid/Hematologic Effects	Lymphoid / hematologic toxicity was observed in rats given ≥3 mg/kg/day and in dogs ~~at ≥3 and~~ given ≥5 mg/kg/day ~~respectively~~. The effects manifested as hypocellularity in bone marrow, thymus and lymph nodes of rats and dogs and reduced cellularity of the ~~thymus, lymph nodes and~~ spleen in rats. This was accompanied peripherally by ~~microscopic~~ evidence of increased red cell turnover and/or mild haemolysis. ~~Peripheral effects included~~ reductions in red blood cells, platelets, basophils, eosinophils, lymphocytes, and increases in neutrophils (in response to GI toxicity).	ICF includes the risk of lymphoid / hematologic toxicity. Protocol includes laboratory assessments (complete blood count [CBC] and coagulation factors [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], exclusion criteria if there is evidence of clinically significant bleeding episodes, monitoring for bruising/infection and dose stopping/modifications criteria (refer to Section 14.7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Effects on reticulocyte counts were variable. Regenerative response in blood cell parameters and microscopic observation of extramedullary haematopoiesis and increased cellularity in the lymph nodes and spleen was evident after up to five weeks off dose. ~~Reversible i~~Increased activated partial thromboplastin time (APTT) ~~time~~ was observed in male rats given ≥1 mg/kg/day and in dogs ~~(≥1 mg/kg/day and~~ given 20 mg/kg/day ~~respectively).~~ A mild decrease in APTT was observed in female rats ~~at~~ given 3 mg/kg/day. ~~Reversible i~~Increases in fibrinogen ~~(1.51X)~~ was observed in dogs ~~dosed at~~ given 20 mg/kg/day. All of these effects were reversible. ~~Regenerative response in blood cell parameters and microscopic observation of extramedullary haemopoiesis was evident after up to 5 weeks off dose.~~	
Reproductive Effects	Animal reproductive studies have not been conducted with GSK2820151. No ovarian changes were observed in toxicology studies of up to 4 weeks duration; however, an assessment of estrous cycling was not conducted. BRD2, BRD3, BRD4 and BRDT have crucial roles in reproduction and development [Paillisson, 2007;	ICF includes the risk of damage to reproductive organs such as testes or ovaries including potential risk to embryofetal development. Protocol (refer to Section 7.3) includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Trousdale, 2004] and would be expected to adversely affect embryofetal development. A compound with a similar pharmacology profile has shown detrimental effects on rat female fertility and embryo-fetal development (EFD) at clinically relevant exposures. This information indicates that GSK2820151 will likely have similar ~~adverse~~ effects on female fertility and EFD ~~embryo-fetal development.~~ Testicular degeneration was observed in ~~both~~ rats given ~~(~~>10 mg/kg/day~~)~~ and dogs given ≥5 mg/kg/day. ~~as well as d~~Disorganized spermatogenesis was also observed in dogs. ~~at ≥5 mg/kg.~~ Secondary changes ~~were evident~~ in epididymides were also evident (hypospermia, degenerate germ cells and/or epithelial vacuolation in both species, and atrophy in dogs only~~,atrophy, vacuolation~~). There was no evidence of reversibility of these findings within a three-week off dose period, but due to the length of the spermatogenic cycle (approximately two months), recovery may occur following a longer off dose period. ~~No evidence of reversibility within 3 week off dose period~~. Reduced prostate weight was observed in rats and	complete) for male subjects. Due to the effects of GSK2820151 on the male reproductive system were observed in pre-clinical settings and potential for GSK2820151 to be present in semen, men should adhere to the contraceptive guidance detailed in the protocol (refer to Section 7.3.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	dogs. Additionally, in rats, decreased secretory content in prostate (dosing at ≥3 mg/kg/day) and in seminal vessels (dosing at 10 mg/kg/day) were observed. These effects were reversible. ~~Reversible reduced prostate weight (rat and dog) & decreased secretory content in prostate (rat ≥ 3 mg/kg/day) and seminal vesicles (rat 10 mg/kg/day) were observed.~~	
~~Liver and Gallbladder~~ Hepatobiliary Effects ~~Hepatobiliary~~	~~Dog:~~Reversible ~~M~~minimal ~~gallbladder~~ vacuolization of the gallbladder and ~~minimal vacuolization of~~ biliary epithelium were observed in dogs ~~dosed at~~ given >10~~20~~ mg/kg/day. ~~Effects were reversible.~~ ~~Rat: Reversible d~~Decreased inflammatory cell infiltrate was observed in rats ~~animals dosed at~~ given ≥3 mg/kg/day and was still evident in some animals after an off dose period of up to 5 weeks. This is considered indicative of the anti-inflammatory pharmacology of BET (bromodomain and extra-terminal) inhibitors..	ICF includes the risk of ~~hepatic/gallbladder~~hepatobiliary effects. Protocol includes hepatic eligibility criteria, laboratory assessments during the study, and dose stopping/modifications criteria for the management of hepatic events (refer to Section 14.3 & Section 14.4).
Lung Effects	Minimal to mild prominent (foamy) alveolar macrophages were observed in rats administered ≥ 1 mg/kg/day. These ~~E~~effects were reversible. The clinical consequences of this finding are unknown.	ICF includes the risk of lung effects. Protocol includes pulmonary function assessments at screening and as clinically appropriate afterwards (subjects with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage, chest radiation) chest x-ray at baseline

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		and dose stopping/modifications criteria for pneumonitis (refer to Section 14.7.1).
Effects on Teeth	Minimal to mild changes related to dentin formation in continuously growing incisors were observed ~~of~~ in rats ~~dosed at~~ given ≥3 mg/kg/day. A ~~M~~marginally increased incidence and/or severity occurred after off dose period. No changes were observed in molar teeth of dogs.	Due to the differences between rodents and human, it is unlikely that these effects of teeth will affect human adults.

Section 5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Rationale for change: The change was made to correct the selection criteria of study population.

Revised Text:

First paragraph

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the GSK2820151 Investigator Brochure [GlaxoSmithKline Document Number 2014N208278_00]. *Approximately 30-50 subjects with relapsed or advanced solid malignancies will be enrolled. All subjects must have failed* refused or otherwise be ineligible for standard therapy, ~~failed up to three lines of cytotoxic therapy,~~ or have a tumor for which there is no standard therapy, *prior to consideration for study. The total number of subjects required will depend upon the number of escalation steps required to reach a MTD.*

Section 5.1 Inclusion Criteria

Rationale for change: The update was made to eligibility criteria for participation of female subject of child bearing potential in the study

Revised Text:

Inclusion criterion #3: Diagnosis of advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable. At time of enrollment, subjects either:

Bullet point 1: ~~R~~refuse or are not candidates for standard curative or palliative therapy,

Bullet point 2: ~~are not candidates for standard curative or palliative therapy,~~

Bullet point 3: have a disease for which no non-investigational therapy exists~~, OR~~

Inclusion criterion #9: A female subject is eligible to participate if she is of

Bullet point 2: Child-bearing potential and agrees to use one of the contraception methods (described in Section 7.3) ~~for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception~~ from the time of the screening pregnancy test until at least 7 months after the last dose of study medication.

Bullet point 3: Negative serum pregnancy test ≤ 7 days prior to first study drug dose, for women of childbearing potential.

Inclusion criterion #10

Male subjects with female partners of child bearing potential must agree to use one of the methods of contraception specified (see Section 7.4). This method must be used from the time of the first dose of study medication until 16 weeks after the last dose of study medication. In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for ~~7 days after stopping~~ 16 weeks following the last dose of study medication.

Section 5.2 Exclusion Criteria

Rationale for change: Changes were made to prevent the hemorrhagic events in the patients while on the study.

Revised Text:

Exclusion criterion #2: Recent prior therapy, defined as follows,

Bullet point a: Any investigational or Food and Drug Administration (FDA)-approved anti-cancer drug within 14 days or 5 half-lives, whichever is longer, prior to the first dose of GSK2820151. ~~Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK2820151. Prior therapy with monoclonal antibodies is permitted so long as 14 days have elapsed since therapy and all therapy-related toxicity has resolved to Grade 1 or less.~~ Note that an investigational drug is defined as a drug without an approved oncologic indication

*Bullet point b:*Any radiotherapy, chemotherapy, targeted therapy or immunotherapy within 14 days or major surgery within 28 days or anti-neoplastic antibody or nitrosoureas/mitomycin C within 42 days prior to the first dose of GSK2820151.

Bullet point c: Anti-androgen (e.g., bicalutamide) therapies for prostate cancer,~~such as bicalutamide~~, must be stopped 4 weeks prior to the first dose of GSK2820151~~enrollment~~. Second-line hormone therapies such as enzalutamide, abiraterone, or orteronel should be stopped 2 weeks prior to enrolment. Subjects with prostate cancer should remain on luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

Exclusion criterion #3

Therapeutic anticoagulation (e.g., warfarin, heparin) must be discontinued 7 days prior to the first dose of GSK2820151 and coagulation parameters must be normalized prior to the first dose of GSK2820151. Low (prophylactic) dose ~~(prophylactic)~~ low molecular weight heparin (LMWH) is permitted. In addition, INR must be monitored in accordance with local institutional practices.

Exclusion criterion #4

Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK2820151 (see Section 7.1.2 for the list of medications).

NOTE: Aspirin up to 100mg PO daily is allowed. Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded except for cases where NSAIDs provide benefit over other analgesics (see Section 7.1.2 for details).

Exclusion criterion #8:

~~Any of the f~~Following electrocardiogram (ECG) findings~~:~~

- Baseline ~~C~~corrected QT (Fridericia's formula) interval (QTcF) ≥450 msec

Exclusion criterion #13:

Subjects with a history of known bleeding disorder(s) or ~~H~~history of clinical significant hemorrhage (~~major~~e.g., gastrointestinal, neurologic) ~~bleeding~~ within the last 6 months.

Section 5.3 Screening/Baseline/Run-in Failures

Rationale for change: Corrections and clarification have been made to this section.

Revised Text:

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently ~~enrolled~~dosed with study medication. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

Section 5.4 Withdrawal/Stopping Criteria

Rationale for change: Corrections and clarification have been made to this section.

Revised Text:

Seventh paragraph deleted

~~All subjects who permanently discontinue study treatment without disease progression will be followed for progression according to the protocol schedule until:~~

- ~~new anti-cancer therapy is initiated~~

- ~~progression~~
- ~~death, or~~
- ~~subject has been followed for 2 years after stopping treatment.~~

Eigth paragraph

All subjects who permanently discontinue study treatment for any reason will be followed for survival and new anti-cancer therapy (including radiotherapy) every 6 months until death, termination of the study by the sponsor, or until the subject has been followed for 2 years. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression. If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).
The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

Section 5.5 Subject and Study Completion

Rationale for change: Corrections and clarification have been made to this section.

Revised Text:

Second paragraph

A subject will be considered to have completed the study 2 years after the last treatment or if the subject dies or is still receiving study treatment or in follow-up at the time the study is closed or terminated, whichever is sooner. Document the cause of death in the eCRF. ~~A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.~~The End of Study eCRF should only be completed when a subject is no longer being followed. The end of the study is defined as the last subject's last visit.

Section 7. MEDICATION, DIETARY AND LIFESTYLE RESTRICTIONS

Rationale for change: Corrections and clarification have been made to this section.

Revised Text:

Section name revised

MEDICATION, ~~LIFESTYLE, AND~~ DIETARY AND LIFESTYLE RESTRICTIONS

Section 7.1.1 Permitted Medications and Non-Drug Therapies

Rationale for change: Minor correction has been made.

Revised Text:

First paragraph

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with erythropoietin, antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Colony-stimulating factors like filgrastim and pegfilgrastim may be used ~~in cycles 2 and beyond~~ as clinically indicated. The only caveat is that subjects should not receive those medications listed as prohibited in Section 7.1.2.1.

Section 7.1.2.1 Prohibited Medications

Rationale for change: The change was made to update the list of drug with a risk of Torsades de Pointes that are prohibited based on the 2017 guidelines mentioned on crediblemeds.org.

Revised Text:

Previous Second paragraph deleted

~~Anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc.) are PROHIBITED from seven days prior to the first dose of study drug through completion of the Final Study Visit. Low dose (prophylactic) anticoagulants are permitted provided that the subject's PT/PTT values meet entry criteria.~~

Two New paragraphs (third and fourth) added

Anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc.) are PROHIBITED from seven days prior to the first dose of study drug through completion of the Final Study Visit. Low dose (prophylactic) anticoagulants are permitted provided that the subject's PT/PTT values meet entry criteria.

Subjects may continue to use aspirin, but doses are not allowed to be greater than 100 mg per day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution, including concomitant use of proton pump inhibitors.

Fifth paragraph

Co-administration of the ~~following~~ medications listed in Table 5 are **PROHIBITED** for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes

(with the exception of **amiodarone** which is prohibited beginning **6 months** prior to Screening through discontinuation from the study. [However, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines]). ~~These medications include (but are not limited to):~~

Table 5 Drugs with a Risk of Torsades de Pointes that are Prohibited[1]

Amiodarone	Dronedarone	Moxifloxacin~~Pimozide~~
Anagrelide	Droperidol	Papaverine~~Procainamide~~
Azithromycin	Erythromycin	Pentamidine ~~Propofol~~
Chloroquine	Escitalopram	Pimozide~~Quinidine~~
Chlorpromazine	Flecainide	Procainamide~~Sevoflurane~~
Cilostazol	Fluconazol	Propofol~~Sotalol~~
Ciprofloxacin	Halofantrine	Quinidine~~Thioridazine~~
Citalopram	Haloperidol	Roxithromycin
Clarithromycin	Ibogaine~~Ibutilide~~	Sevoflurane
Cocaine	Ibutilide~~Levofloxacin~~	Sotalol
Disopyramide	Levofloxacin~~Methadone~~	Sulpiride
Dofetilide	Levomepromazine ~~Moxifloxacin~~	Sultopride
Domperidone	Levosulpiride	Terlipressin
Donepezil	Methadone~~Pentamidine~~	Thioridazine

Data Source: crediblemeds.org revision date ~~4 May 2015~~ 09 January 2017.

Drugs not available/used in the US have been omitted.

[1]The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

Previous fifth paragraph deleted

~~At time of screening, if a subject is currently receiving any of the listed prohibited medications/substances, the medication or substance must be discontinued for a period of 5 half lives (or at least 14 days, whichever is longer) prior to the administration of the first dose of study drug in order for the subject to meet study eligibility.~~

Sixth paragraph

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (up to a maximum dose of 0.25 mg daily) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class (i.e. dolasetron and granisetron are not permitted).

Section 7.1.3 Cautionary Medications

Rationale for change: The change was made to update the list of drug with a risk of Torsades de Pointes which are permitted for co-administration with extreme caution based on the 2017 guidelines mentioned on crediblemeds.org.

Revised Text:

Table 6 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution[1]

AlfuzosinAlfuzosin	FoscarnetIloperidone	PerphenazineRanolazine
ApomorphineApomorphine	GemifloxacinIsradipine	PipamperoneRilpivirine
AripiprazoleAripiprazole	Hydrocodone ERLithium	PromethazineRisperidone
Artenimole+piperaquineAtazanavir	IloperidoneMifepristone	RilpivirineSaquinavir
AsenapineAtomoxetine	ImipramineMirabegron	RisperidoneTacrolimus
AtomoxetineBedaquiline	IsradipineMirtazapine	SaquinavirTelavancin
BedaquilineClomipramine	LeuprolideMoexipril/Hydrochlorothiazide (HCTZ)	SertindoleTelithromycin
BuprenorphineClozapine	LithiumNicardipine	SolifenacinTetrabenazine
ClomipramineDesipramine	MelperoneNorfloxacin	TacrolimusTizanidine
ClozapineDexmedetomidine	MifepristoneNortriptyline	TelavancinTolterodine
CyamemazineDihydroartemisinin+piperaquine	MirabegronOfloxacin	TelithromycinToremifene
DegarelixDolasetron	MirtazapineOlanzapine	TetrabenazineTrimipramine
DelamanidFamotidine	Moexipril/ hydrochlorothiazide Ondansetron	TiaprideVardenafil
DesipramineFelbamate	NicardipineOxytocin	TizanidineVenlafaxine
DexmedetomidineFingolimod	NorfloxacinPaliperidone	TolterodineZiprasidone
EfavirenzFoscarnet	NortriptylinePasireotide	Trimipramine
Ezogabine	OfloxacinPerflutren lipid microspheres	Tropisetron
FamotidineGemifloxacin	OxytocinPromethazine	Vardenafil
FelbamateGranisetron	PaliperidoneQuetiapine	Venlafaxine
Fingolimod	Pasireotide	Zotepine
Flupentixol	Perflutren lipid microspheres	Perphenazine

Data Source: crediblemeds.org revision date 04 May 2015 09 January 2017.

[1]The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

Note: This list is not exhaustive. Drugs not available/used in the US have been omitted

Fifth paragraph

GSK2820151 may also interact with organic anion transporter 3 (OAT3). Substrates of OAT3 include agents such as Penicillin G, and indomethacin, and ciprofloxacin. While co-administration of these agents with GSK2820151 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Section 7.3 Lifestyle Restrictions (Contraception)

Rationale for change: Corrections and clarification were made to this section.

Revised Text:

New heading, 'Section 7.3 Lifestyle Restrictions (Contraception)' replaced old heading 'Section 7.3 Female Subjects' which was then moved to third level heading as Section 7.3.1 Female Subjects

Section 7.3.1 Female Subjects

Rationale for change: The change was made to add criteria for pregnancy in female subjects of childbearing potential and also to clarify the hormonal means of birth control.

Revised Text:

First paragraph

Female subjects of childbearing potential must not become pregnant during the trial and for 7 months after stopping study medication and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of ≤ 1%.

Second paragraph, Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are ~~not~~ NOT acceptable methods of contraception.

Third paragraph, Contraceptive Methods with a Failure Rate of ≤1%

Bullet point 1: Non-hormonal ~~i~~intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label

Fifth paragraph

All ~~H~~hormonal means of birth control such as oral, injectable, dermal, subdermal or topical contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

Section 7.3.2 Male Subjects

Rationale for change: The change was made to clarify the contraceptive measures to be taken by the male population.

Revised Text:

First paragraph

Bullet point 1: Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview, **OR**

Bullet point 2: Condom use ~~plus~~PLUS partner use of a highly effective contraceptive (≤1% rate of failure per year) such as occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/film/cream/suppository), or intrauterine device. **OR**

Bullet point 3: Condom use PLUS partner use of hormonal birth control such as contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches.

> The above list does not apply to male subjects with a female partner of child bearing potential who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. ~~Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject.~~Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are ~~not~~NOT acceptable methods of contraception

Bullet point 4: In addition, male participants must refrain from donating sperm for duration of study and until 16 weeks after the last dose of study drug

Section 8.1 Time and Events Table

Rationale for change: Corrections and clarifications were made to this section.

Revised Text:

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X	X	X			X	X	X	X	X			Daily									
Review subject diary	Diary not required when dosed									X							X		X		X	X	X	X		

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
	in clinic.																									
Safety																										
Pregnancy test/ testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp, O2 saturation	X	X	X				X		X					X		X		X		X	X	X	X		X
Pain (using Wong-Baker Faces Pain Rating scale)		X	X	X				X		X					X		X		X		X	X	X	X		X
Weight and	Height at	X	X							X							X		X		X	X	X	X		X

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
height	SCR only																									
Chest x-ray		X																								
Pulmonary function tests (spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry)	All patients will have PFTs at baseline; afterwards as clinically indicated (e.g., in patients with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage and chest radiation etc)	X																								
Adverse events		*continuous from signing of informed consent*																								
Concomitant medications		*continuous from signing of informed consent*																								
Laboratory assessments: For details please see following tables																										
Tests		X	X	X				X		X					X		X		X		X	X	X	X	X	X
Cardiac Monitoring																										

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																						EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Echocardiogram	Within 35 days of first dose	X																			X		X		X	X
12-lead ECGs (Triplicate)	Triplicate SCR ECGs within 35 days of first dose. For timing of triplicate ECGs on O days, see Table 9 and Table 10. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O	O/~~X~~	X		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at	X	X				X						X					X					X			

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																							EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
	least 60 min predose.																									
Telemetry	Start at least 60 min predose and for at least 48 h.		X	X																						
Efficacy																										
Cross-sectional (Computed tomography [CT] or magnetic resonance imaging [MRI]), functional (Positron emission tomography [PET]), or nuclear (bone scan) imaging	Appropriate imaging modality should be selected by the investigator depending on disease histology and location. SCR assessment within 2 weeks of first dose. Target lesions to be identified at SCR and followed. See Section 14.8.1 for guidelines.	X																					X		X	X

Assessments	Notes	SCR	Refer to Section 8.4.2 for visit windows.																						EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see Table 9 and Table 10																									
PK and biomarker samples			X	X			X						X					X					X			
Samples for mRNA		X	X	X														X								X
LPS blood sample			X																							
PK Urine samples			X															X								
Pharmacogenomics (PGx)																										
PGx sample			X																							
FOLLOW-UP PHASE																										

Table 8 Time and Events: Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	W1			W2		W3	W4	W5	W7	W9	q4W	q8W	EOT
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP-9	W1D1, W1D2: local lab sample 3X/24h; central lab sample 1X/24h. All other timepoints including ~~U~~unscheduled collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X	X		X		X	X
Hematology		X	X		X	X	X	X[1]	X	X	X	X	X		X
Clinical chemistry		X	X		X	X	X	X	X	X	X	X	X		X
Pancreatic		X	X		X	X		X		X	X	X	X		X
Coagulation		X	X		X	X		X		X	X	X	X		X
Factor VII Assay	Also perform if PT, INR or aPTT are ≥1.5XULN, or in case of bleeding event	X						X		X					
Creatine phosphokinase		X	X		X	X		X		X	X	X	X		X
Liver chemistry		X	X		X	X	X	X	X	X	X	X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X	X		X		X	X	X	X		X
c-peptide and 1,5 –Anhydroglucitol (1,5 AG)	Will be performed at central lab if not available at local lab	X	X							X		X		X	
Hemoglobin A1c		X	X							X		X		X	
Fasting lipids		X	X							X		X		X	X
Thyroid monitoring	Thyroid stimulating hormone (TSH), free T3, free T4. If TSH is abnormal at W1D1, continue monitor TSH, free T3 and free T4 going forward	X	X							X		X		X	X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Urinalysis		X	X							X		X		X	X
Pregnancy test, females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X							X		X	X		X
Testosterone, males	Complete and free testosterone at SCR; free testosterone thereafter	X	X							X		X	X		X
CK, CK-MB	Predose and 12-18 h post dose		X	*as clinically appropriate*											
Safety Cytokines	This is collected as part of the Predose PK sample and is sent to Myriad via Covance.	X	*as clinically appropriate following fever*												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X													

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

1. If any parameter (i.e., platelets) shows a downward trend, additional analyses should be performed within 2-3 days to monitor.

Section 8.2.2 Visit Windows

Rationale for change: Corrections and clarification were made to this section.

Revised Text:

Week 2 to Week 49**:** Based on subject and clinic schedule, assessments can be ±3 days.

~~**Week 4 to Week 9:** Clinic visits can be scheduled ±3 day.~~

Discontinuation visit: should be 14 ~~to 28~~ days from last dose of study drugs. If a subject is unable to return to the clinic due to hospitalization, site staffs are encouraged to telephone the subject for assessment of adverse events.

Section 8.3.4 Pain and Section 8.3.5 Echocardiogram

Rationale for change: Corrections were made to this section.

Revised Text:

Section 8.3.4 Pain will be assessed using Wong-Baker Faces Pain Rating scale (Appendix 11). Echocardiogram split into two sections: **Section 8.3.4 Pain** and **Section 8.3.5 Echocardiogram**

Section 8.3.5 Echocardiogram

Rationale for change: Corrections were made to this section.

Revised Text:

First paragraph

For all subjects, trans-thoracic echocardiograms (TTEs) will be performed at screening and at assessment times as outlined in Table 7. TTEs should be evaluated and compared to baseline by the same reader. ~~Copies of all TTE scans performed on subjects who experience an absolute decrease >10% in left ventricular ejection fraction (LVEF) compared to baseline concurrent with LVEF < LLN will be required by GSK for review.~~

Second paragraph

~~TTE~~ ECHO data may be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying ~~TTE~~ ECHO scans are provided in the Study Procedure Manual (SPM) ~~Laboratory Manual~~.

Section 8.3.6 Safety Electrocardiograms (ECG)

Rationale for change: Minor correction was made to this section.

Revised Text:

Safety ECGs will be performed at the time points specified in Table 7 using a standard 12-lead ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Details will be provided in the ~~Laboratory Manual~~SPM.

Section 8.3.6.1 Routine ECG Monitoring

Rationale for change: Minor correction was made to this section.

Revised Text:

Last paragraph

ECG data may be transferred and reviewed by an independent central reviewer. Instructions for submission of ECGs are provided in the ~~Laboratory Manual~~ SPM.

Section 8.3.9 Clinical Safety Laboratory Assessments

Rationale for change: Minor correction was made to this section.

Revised Text:

Last paragraph

All laboratory ~~tests with values~~results that are considered by the investigator clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be recorded on the eCRF as AEs. In addition, these clinically significant abnormal laboratory results should be followed until the abnormality resolves or is determined to be stable. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Section 8.3.10 Troponin Measurement

Rationale for change: The change was made for clarification on Troponin sampling and analysis. Minor corrections were also made to this section.

Revised Text:

~~Two samples for troponin will be collected at each time-point as outlined in **Table 8**~~. At W1D1 and W1D2 three local lab troponin samples (8hrs apart) should be drawn per day but only 1 central lab sample should be drawn per day. At other time-points (including unscheduled visit) only two samples should be drawn; 1 for local lab analysis and 1 for central lab analysis. Troponin T will be assessed at a central laboratory as a means of consistent evaluation across all subjects~~.~~ Whereas ~~A~~ second sample~~, will be~~ assessed at a local laboratory, will be used for purpose~~s~~ of subject management. Whenever possible, troponin T will be assayed by the local laboratory. However, either troponin I or troponin T may be assessed at a local laboratory. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study.

Section 8.4.2 Urine Sample Collection for Pharmacokinetics

Rationale for change: The change was made for clarification on urine sampling and analysis for PK.

Revised Text:

Second paragraph

The actual date and time of each urine sample collection will be recorded. In addition, pooled urine pH, the total volume of the pooled urine and the weight of the pooled urine will be measured and recorded in the eCRF.

Section 8.6 Efficacy

Rationale for change: Corrections and clarification were made to this section.

Revised Text:

First paragraph,

Bullet point 1: Lesion assessment ~~method and timing, evaluation of disease, disease progression and response criteria~~ will be conducted according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009] as outlined below and in Appendix 8.

Bullet point 3: The baseline disease assessment will be completed within 2 weeks prior to the first dose of GSK2820151, then every 8 weeks starting W1D1 thereafter, and at the final study visit. See the Time and Events Table (Section 8.1) for the schedule of assessments of anti-cancer activity.

Section 11.4.2 Interim Analysis

Rationale for change: Clarification was made to this section.

Revised Text:

Last paragraph added

An interim analysis of the pharmacodynamic data will be conducted once an appropriate amount of data has been collected and has been batched for analysis. Interim analyses of the pharmacodynamic data may be conducted throughout the duration of the study.

Section 14.4 Appendix 4: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

Rationale for change: Correction was made to this section.

Revised Text:

Text deleted-fourth Paragraph

~~**Background Information on Drug Restart/Rechallenge**~~

Section 14.7.1 Dose Adjustments for Toxicity

Rationale for change: Update made in the light of new information.

Revised Text:

Table 12 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
QTcF	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN	• ~~Evaluate immediately for~~Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin within 24-48 hours or as soon as possible. • If the subject is asymptomatic and repeat value is within the normal range, the subject may continue GSK2820151 with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. • If the repeat value remains > ULN AND the subject is asymptomatic, hold GSK2820151, refer to a cardiologist, and contact the GSK Medical Monitor. May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor. • If the subject is symptomatic (symptoms consistent with acute coronary syndrome) OR the troponin level is at or above the threshold for mycocardial infarction (MI) according to local lab parameters, discontinue GSK2820151 permanently and refer the subject immediately to a cardiologist or emergency medical facility for appropriate medical care.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
LVEF	Ejection fraction below the institution's lower limit of normal (LLN) AND An asymptomatic, absolute decrease of >10% in LVEF compared to baseline	Withhold GSK2820151 and repeat evaluation of LVEF within 2 weeks If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution, whichever is longer.
	Grade 3 or 4	Permanently discontinue GSK2820151. Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution, whichever is longer.
Hypo- and Hyperglycemia Note: for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE version v4.03 Grade 1-5	~~(Mild)~~ Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)	• Monitor fasting and preprandial glucose. • If persistent over 2 repeats over 3-4 weeks, consult Diabetologist and consider starting metformin

	~~(Moderate to Severe) Fasting blood glucose <70 mg/dL OR any blood glucose >250 mg/dL~~
	
	Any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)
		• Withhold~~Hold~~ GSK2820151 and instruct subject to notify investigator immediately.
		  • ~~If a blood glucose >250 mg/dL is observed, the subject should be evaluated~~ Monitor for ketoacidosis as clinically indicated.
		  • If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist . Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve.
		  ~~o This may necessitate inpatient management.~~
		  ~~o The action of insulin or other antihyperglycemic agents should be restored as study medication is cleared. If an antihyperglycemic agent is administered, then the subject should be observed closely for rebound hypoglycemia as the study medication is cleared.~~

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		~~○ Intravenous insulin treatment is recommended.~~ • May consider restarting GSK2820151 at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.
	Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	Withhold GSK2820151 Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes, may restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.
Diarrhea	Grade 3	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • ~~H~~Withhold GSK2820151 ~~and discuss with GSK Medical Monitor~~ until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis • If diarrhea recovers to ~~less than~~ ≤ Grade 1 ~~2~~, discuss with medical monitor; consider resuming treatment at the same or lower dose based on clinical judgement.

Mucositis	Grade 3 or 4	• Above, plus systemic opiate administration as needed.
		  • Consider IV hydration and hospital admission as appropriate.
		  • For mucositis >Grade 3, withhold GSK2820151 until mucositis is <Grade 1 and resume the same dose of GSK2820151. If mucositis >Grade 3 recurs, withhold GSK2820151 until mucositis is <Grade 1, then reduce GSK2820151 one dose level. If mucositis >Grade 3 recurs a third time at reduced dose, discontinue GSK2820151 permanently.
		~~• May restart GSK2820151 at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.~~

Pneumonitis	Grade 1	~~• Continue GSK2820151 at current dose.~~ • Consider evaluation by pulmonologist. ~~•~~ Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). If any decline is observed in O_2 saturation, withhold study drug, repeat chest x-ray to determine if progression of pneumonitis has

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		occurred and consult pulmonologist.~~Repeat evaluations every 8-12 weeks until return to baseline.~~ • Obtain high-resolution computed tomography (CT) scan of the chest if possible.

	Grade 2	• ~~Hold GSK2820151 until recovery to < Grade 1~~, then reduce dose by at least 25%.
		• ~~Consider~~ Must be evaluated~~ion~~ by pulmonologist.
		  • Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to baseline.
		  • Obtain high-resolution chest CT if possible.
		  • Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL).
		  • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated.
		• Withhold GSK2820151 until recovery to < Grade 1, then reduce dose by at least 25%. Discontinue GSK2820151 if no recovery to ≤Grade 1 within 4 weeks. ~~May consider escalation to pre-event dose after discussion with GSK Medical Monitor~~

	Grade 3 or 4	• ~~Hold~~ Discontinue GSK2820151 and refer for evaluation by pulmonologist
		  • Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to baseline.
		  • Obtain high-resolution chest CT if possible.
		  • Bronchoscopy with biopsy and/or BAL is recommended.
		  • Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.
		• Rechallenge Guidelines
		  • Grade 3: ~~Hold~~ Withhold GSK2820151 until recovery to < Grade 1. Discontinue GSK2820151 if no recovery to < Grade 1 within 4 weeks. May consider restarting GSK2820151 at a reduced dose after discussion with GSK Medical Monitor if

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		there is clinical benefit. • Grade 4: Rechallenge with GSK2820151 is not permitted
Thrombocytopenia	Grade 1 (platelets <LLN to ≥75,000/mm^3) or Grade 2 (platelets <75,000 to ≥50,000/mm^3) ~~Count ≥ 50,000)~~	• Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000 to ≥25,000/mm^3) ~~Count 25,000 – 50,000)~~	~~• After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider reduced daily dosing or dosing on alternate days). Monitor CBC at least twice a week, more frequently if necessary~~ Withhold GSK2820151 and check aPTT, PT, and INR. Monitor CBC and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Withhold GSK2820151 until thrombocytopenia has resolved to ≤ Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued permanently or restarted at further lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur to the same level following a second rechallenge, drug will be discontinued permanently.
	Grade 4 (~~Count~~ platelets≤25,000) or any moderate to severe bleeding accompanied by drug related thrombocytopenia	~~Interrupt study medication and monitor CBC every 2-3 days~~ Withhold GSK2820151 and check aPTT, PT, and INR. Monitor CBC and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Withhold GSK2820151 until thrombocytopenia has resolved to ≤ Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued permanently. If platelet count does not recover to ≥25,000/mm^3 (Grade 3) within 7 days and ≥50,000/mm^3 (Grade 2) within 14 days, GSK2820151 should be permanently discontinued.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		Any subject requiring transfusion support, GSK2820151 should be permanently discontinued. • ~~If platelet counts recover to Grade 2, discuss with medical monitor resuming treatment at the same or adjusted dose based on sound clinical judgement.~~ • ~~Platelet transfusion is allowed based on institutional guidelines. In case of platelet transfusion, hold drug for at least 7 days from day of transfusion, and if platelet counts recover to Grade 2 consider initiating treatment at a lower dose using sound clinical judgement and after consulting with the GSK medical monitor.~~ • ~~Discontinue treatment if drug has to be held for >14 days or greater than 2 dose reductions are required.~~
All Other Toxicity*	1	• Continue dosing with no change
	2	• Continue dosing with no change OR • ~~Hold~~Withhold GSK2820151 for up to 1 week for toxicity to be < Grade 2, then continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	3	• 1st episode: ~~Hold~~Withhold dose for one week intervals until ≤ drug-related Grade 2, then restart with no change. • 2nd episode: Utilize an alternative, less frequent schedule or reduce by one dose level. • If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.

*Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for certain AEs as defined in Section 4.2.5.

Section 14.10 Appendix 10: Collection of Pregnancy Information

Rationale for change: Correction was made to this section.

Revised Text:

Bullet point 2: Information will be recorded on the appropriate form and submitted to GSK within ~~2 weeks~~ 24 hours of learning of a subject's pregnancy.

Section 14.12 Appendix 12: NYHA Functional Classification System for Heart Failure

Rationale for change: Added NYHA classification which was missing in the previous versions.

Revised Text:

The New York Heart Association (NYHA) Functional Classification [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of four categories based on the level of limitation experienced during physical activity:

Class	**Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A Phase I Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK2820151 in Subjects with Advanced or Recurrent Solid Tumors

Compound Number:	GSK2820151
Development Phase	I
Effective Date:	15-DEC-2014

Authors:

PPD

SPONSOR SIGNATORY:

PPD

Christopher Carpenter, MD, PhD
VP & Head, Cancer Epigenetics DPU

12/15/2014
Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After Hours Contact Information	Site Address
Primary Medical Monitor	PPD MD/PhD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA
Secondary Medical Monitor	PPD MD/PhD			GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): 124949

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 201893

Rationale

The Bromodomain (BRD) and Extra-Terminal (BET) family is comprised of four different proteins that bind via their bromodomains to acetylated histone tails in order to regulate transcription, cell growth, and survival. In preclinical models, small molecules that inhibit the binding of BET proteins to histones have been associated with potential therapeutic benefit for multiple human malignancies. The study drug, GSK2820151, is a BET inhibitor arising from a distinct structural class to that previously progressed to clinical studies. GSK2820151 potently inhibits tumor growth *in vitro* and *in vivo* in animal models. This first time in human (FTIH), open-label, dose escalation study will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK2820151 in subjects with advanced or recurrent solid tumors.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• **To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK2820151 in subjects 18 years or older with advanced or recurrent solid tumors.**	• **Adverse events (AEs), serious adverse events (SAEs), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, electrocardiogram (ECG), cardiotoxicity, gastrointestinal, etc.)**
Secondary	
• To determine a recommended Phase 2 dose (RP2D) of GSK2820151 in subjects 18 years or older.	• Safety profile (AEs, SAEs, dose-limiting toxicities [DLTs]), clinical response, and PD data
• To characterize the pharmacokinetics (PK) of GSK2820151 in subjects 18 years or older.	• PK parameter values for GSK2820151 following single and repeat-dose oral administration in subjects 18 years or older.
• To evaluate the effect of treatment with GSK2820151 on tumor growth and subject survival.	• Objective response rate (ORR) by various imaging modalities and progression free survival (PFS).
• To evaluate cardiac safety, including the potential for corrected QT interval (QTc) prolongation, of GSK2820151 and to assess PK/QTc relationship.	• Changes in cardiac safety including QTc following single and repeat-dose oral administration of GSK2820151.
Exploratory	
• To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK2820151 and safety and efficacy parameters.	• Dose-related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in peripheral blood samples.

Objectives	Endpoints
• To evaluate systemic and *ex vivo* on-target BET inhibitory effects	• Changes from baseline and dose/response relationship in *ex vivo* lipopolysaccharide (LPS)-induced cytokines, including Interleukin 6 (IL-6), in whole blood, and systemic cytokines, including IL-6.
• To identify potential indicators of sensitivity or response to GSK2820151.	• Transcriptomic studies of blood; correlation of baseline genetic and genomic profiles with response.

Overall Design

This study is a single-arm, open-label, dose-escalation study to determine the MTD (and a RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK2820151. Eligible subjects with advanced or recurrent solid tumors will be enrolled in the dosing cohorts until an MTD is established. For a schematic representation of the study, please refer to Figure 2.

Treatment Arms and Duration

This is a single-arm study in which all subjects will receive the investigational agent. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. The duration of study will depend on recruitment rates and the timing of subjects' duration on study (withdrawal rates due to toxicity or progression), with an approximate duration of 3 years.

Type and Number of Subjects

Approximately 30 to 50 subjects with will be enrolled in the study. The study population will be adults, with advanced or recurrent solid malignancy, who either:

- refuse standard therapy,
- are not candidates for standard therapy,
- have a disease for which no non-investigational therapy exists, OR
- have progressed on prior therapy (up to three lines of prior cytotoxic agents are permitted).

The total number of subjects required will depend upon the number of escalation steps required to reach a MTD.

Analysis

After each dosing cohort, a Neuenschwander Continual Reassessment Method (N-CRM) [Neuenschwander, 2008] analysis will be used to recommend the next dose level based on observed dose-limiting toxicities (DLTs). Dose escalation decisions will be based on

the totality of clinical safety assessment based on a combination of reported safety events, N-CRM recommendation, as well as pharmacokinetic and pharmacodynamic data.

All data will be pooled and descriptive analyses summarized and listed by cohort at study conclusion. No formal statistical hypotheses will be tested. Analyses will be descriptive and exploratory.

Measurements

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There will be extensive PK sampling during this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Blood samples will be collected for analysis of protein biomarkers (cytokines and acute phase proteins) and messenger ribonucleic acid (mRNA). LPS induction of cytokines in whole blood will be assessed.
- **EFFICACY MEASUREMENTS**: ORR and PFS.
- **SAFETY MEASUREMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events will be performed. Stringent cardiac safety monitoring will be required, consisting of:
  - ≥ 48 hours of telemetry following the first dose (necessitating overnight stays in a research facility)
  - 24 hours of ambulatory cardiac (Holter) monitoring in Week 1, Week 2, Week 4, and Week 9
  - Triplicate 12-lead ECGs prior to dosing on selected days and prior to drawing PK samples on serial PK sampling days.

  Extensive laboratory testing includes standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels. Troponin, C-peptide, 1,5-anhydroglucitol, glycosylated hemoglobin (hemoglobin A1c), and thyroid monitoring will also be performed.

2. INTRODUCTION

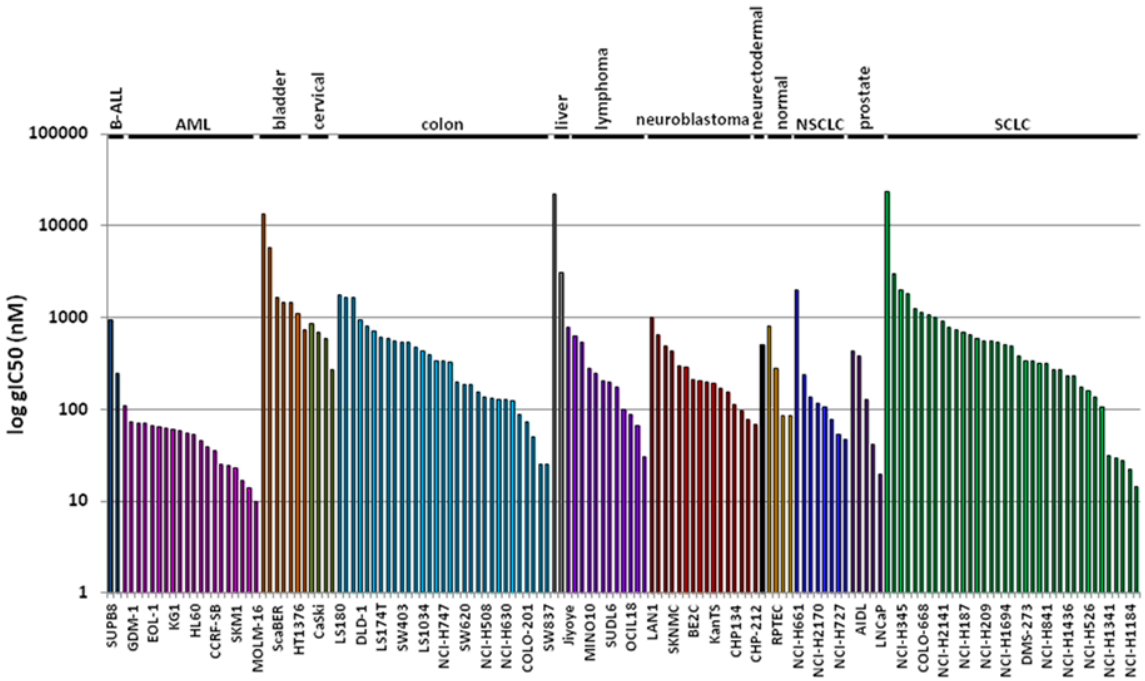
GSK2820151 is a novel, orally available inhibitor of the Bromodomain (BRD) and Extra-Terminal (BET) family of bromodomain-containing transcriptional regulators that is being developed for treatment of multiple solid malignancies.

2.1. Study Rationale

The aim of this study is to establish a maximum tolerated dose for the BET inhibitor GSK2820151 in subjects with refractory, advanced solid malignancies where prognosis is particularly poor with limited effective treatment options. Preclinical studies have shown that small molecule-based inhibition of BET protein binding to chromatin with GSK2820151 inhibits proliferation of multiple solid tumor-derived cancer cell lines and results in significant anti-tumor activity in animal models of advanced disease [Chaidos, 2014; Wyce, 2013].

Consistent with the published literature, GSK2820151 inhibits proliferation and induces a cytotoxic response in cell lines across a wide range of solid tumor types (Figure 1). GSK2820151 inhibits growth in a broad spectrum of human solid cancer and hematological (heme) cell lines. These include NUT (Nuclear protein in testes) midline carcinoma (NMC), non-small cell lung cancer (NSCLC), neuroblastoma, cervical cancer, prostate cancer, small cell lung cancer (SCLC), colorectal cancer (CRC), acute myeloid leukemia (AML), multiple myeloma (MM), and lymphoma. By way of example in the largest panel of cell lines tested (n=149), eighty seven percent are highly sensitive to GSK2820151, exhibiting growth IC_{50} (gIC_{50}) values below 1.0 µM (Figure 1)

Figure 1 Effect of GSK2820151 on the growth of human tumor-derived cell lines



Bromodomains (BRDs) are found in a variety of proteins that recognize and bind to acetylated histone tails [Dhalluin, 1999]. This binding affects chromatin structure and facilitates the localization of transcriptional complexes to specific genes, thereby regulating gene transcription and messenger ribonucleic acid (mRNA) elongation [Dey, 2003; Jang, 2005]. The BRD extra-terminal (BET) family of BRD proteins includes the BRD2, BRD3, BRD4, and BRDT proteins.

BET proteins have been shown to be involved in the regulation of transcription, cell growth, and survival. In addition, BRD4 has been shown to be directly involved in regulation of the cell cycle, as it remains associated with chromosomes through mitosis, specifically at the transcription start site (TSS) of genes expressed at the M/G1 phase of the cycle [Dey, 2009]. BRD4 is also a critical mediator of transcriptional elongation, functioning to recruit the positive transcription elongation factor complex (P-TEFb) [Itzen, 2014; Patel, 2013]. BRD4 inhibition, through blocking P-TEFb recruitment to chromosomes, results in decreased expression of growth-promoting genes [Hargreaves, 2009].

The investigational agent GSK2820151 is a potent inhibitor of the BET family of proteins. The crystal structure of GSK2820151 in complex with the bromodomain 1 of BRD4 reveals the compound to bind as a histone mimetic. This binding mode has been shown previously for other compounds to inhibit the assembly of the transcriptional complex and the subsequent gene expression response [Nicodeme, 2010].

The role of BET proteins in malignancy is best demonstrated in Nuclear Protein in Testes (NUT) midline carcinoma (NMC), a rare, aggressive, and invariably lethal tumor with a median overall survival of 6.7 months [Bauer, 2012]. NMC is triggered by a translocation between the NUT gene and one of the BRD genes (typically BRD3 or BRD4) [French, 2008]; the resulting fusion oncoprotein is retained in the cell nucleus via interactions with chromatin [Yan, 2011]. Treatment of patient-derived NMC lines with small molecule BET inhibitors leads to rapid growth inhibition and differentiation of cells to a non malignant phenotype. This has led to the further clinical investigation of compounds for this patient population.

While NMC is the prototypic BET-driven malignancy, other tumor types have been found to require functional BET for growth and progression [Fiskus, 2014; Trabucco, 2014; Asangani, 2014]. Studies in leukemia and multiple myeloma (MM) cell lines have shown that small molecule inhibition of BET protein binding to chromatin can directly block expression of the gene *myc* and its downstream transcriptional functions, resulting in significant anti-tumor effects [Delmore, 2011; Mertz, 2011]. GSK2820151 has been studied extensively in cell culture and has been demonstrated to inhibit the growth of multiple solid tumor cell lines apart from NMC, including those derived from cancer of the bladder, breast, cervix, colon/rectum, prostate, and lung (see Figure 1 as well as investigator's brochure [IB], Section 5.2.1.1 [GlaxoSmithKline Document Number 2014N208278_00]). GSK2820151 has also demonstrated efficacy after oral administration in mouse xenograft models of SCLC and NMC (see IB, Section 5.2.1.2 [GlaxoSmithKline Document Number 2014N208278_00]). Based on these observations, administration of GSK2820151 to humans is expected to have potential therapeutic applications in a broad array of solid malignancies.

Importantly, while the biochemical and phenotypic properties of GSK2820151 are comparable to those reported for BET inhibitors under clinical evaluation from the

benzodiazepine class, this agent is the first of its structural class to enter clinical trials. As such differential human pharmacokinetics, pharmacodynamics, or overall safety profile for GSK2820151 may provide beneficial improvements in therapeutic index for patients. It is on this basis that clinical trials with GSK2820151 are being proposed.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• **To determine the safety, tolerability and maximum tolerated dose (MTD) in subjects 18 years or older with advanced or recurrent solid tumors.**	• **Adverse events (AEs), serious adverse events (SAEs), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, electrocardiogram (ECG), cardiotoxicity, gastrointestinal, etc.)**
Secondary	
• To determine a recommended Phase 2 dose (RP2D) of GSK2820151 in subjects 18 years or older.	• Safety profile (AEs, SAEs, dose-limiting toxicities [DLTs]), clinical response, and PD data
• To characterize the pharmacokinetics (PK) of GSK2820151 in subjects 18 years or older.	• PK parameter values for GSK2820151 following single and repeat-dose oral administration in subjects 18 years or older.
• To evaluate the effect of treatment with GSK2820151 on tumor growth and subject survival.	• Objective response rate (ORR) by various imaging modalities and progression free survival (PFS).
• To evaluate cardiac safety, including the potential for corrected QT interval (QTc) prolongation, of GSK2820151 and to assess PK/QTc relationship.	• Changes in cardiac safety including QTc following single and repeat-dose oral administration of GSK2820151.
Exploratory	
• To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK2820151 and safety and efficacy parameters.	• Dose-related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in peripheral blood samples.
• To evaluate systemic and *ex vivo* on-target BET inhibitory effects	• Changes from baseline and dose/response relationship in *ex vivo* lipopolysaccharide (LPS)-induced cytokines, including interleukin 6 (IL-6), in whole blood, and systemic cytokines, including IL-6.
• To identify potential indicators of sensitivity or response to GSK2820151.	• Transcriptomic studies of blood; correlation of baseline genetic and genomic profiles with response.

4. STUDY DESIGN

4.1. Overall Design

This study is a single-agent, open-label, dose-escalation study to determine the MTD (and RP2D), based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK2820151. Eligible subjects with advanced or recurrent solid tumors will be enrolled in the dosing cohorts until MTD is established. All subjects will receive study drug. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent (for specific stopping criteria, see Section 5.4). The duration of study will depend on recruitment rates and the timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

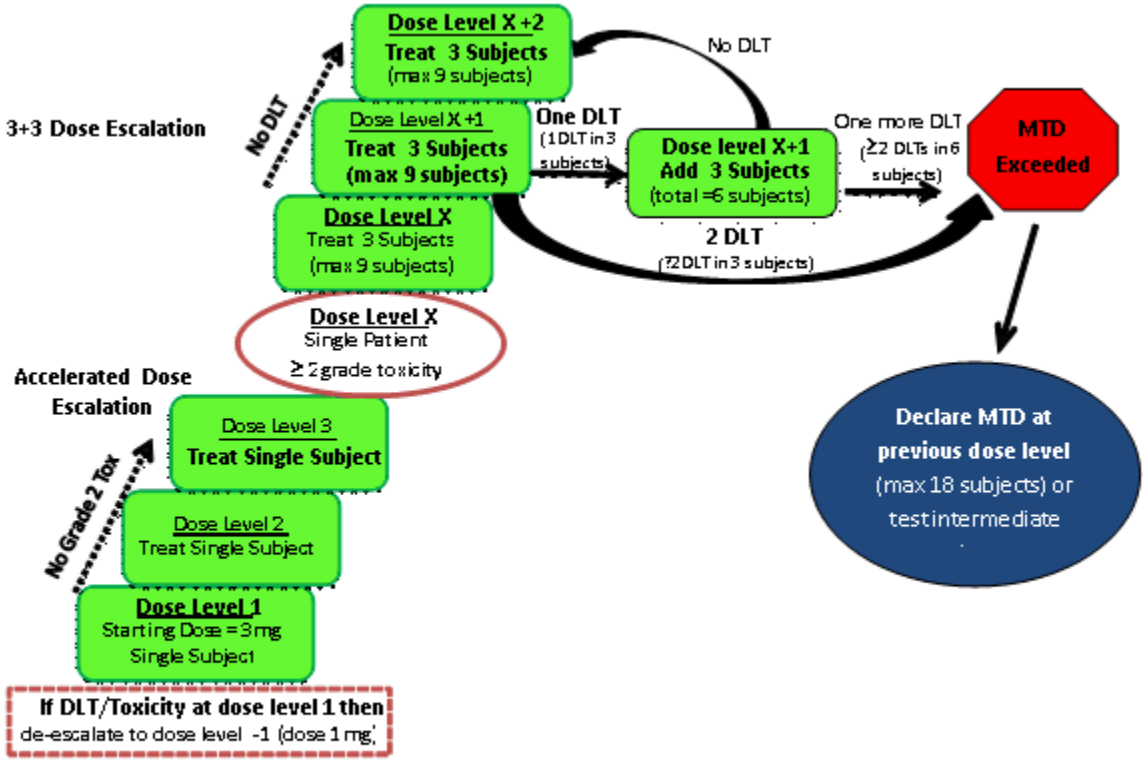
4.2. Dose Escalation and Duration of Study

This study will utilize an accelerated dose escalation phase in order to minimize sub-optimal drug exposures, followed by a conventional 3+3 dose escalation phase to achieve MTD. At least one and up to six subjects will be recruited per cohort. Initially, one subject per dose cohort will be recruited until the first instance of a ≥ Grade 2 drug related non-hematological toxicity. Further cohorts will be recruited in blocks of three subjects. Additional subjects may be enrolled at previously cleared dose levels in order to obtain further data for PK and/or PD analysis. A maximum of six subjects will be assigned to any single dose. Once MTD is determined, up to 12 additional subjects (18 subjects total at MTD) may be enrolled to collect additional safety data (Figure 2). The total duration of study for each subject will be dependent upon the safety, tolerability and efficacy of GSK2820151.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the predicted optimal dose from the Neuenschwander Continual Reassessment Method (N-CRM) analysis, a type of Bayesian adaptive dose-escalation scheme (see Section 11.2). The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The DLT information of all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

The RP2D will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile, and available PD data generated from all subjects (Table 2). If necessary alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

Figure 2 Dose Escalation Scheme



(Dose increase at any dose escalation will be ≤2 fold.)

4.2.1. Planned Dose Levels

Projected dose levels are 3 mg, 6 mg, 12 mg, 20 mg, 40 mg, 60 mg, 100 mg, 150 mg, 200 mg, and 300 mg. Additional doses and schedules may be explored based on emerging safety, PK, and PD data.

4.2.2. Accelerated Dose Escalation

One subject per dose level in the accelerated dose escalation phase will be treated to minimize suboptimal drug exposures, starting with Dose Level 1 and continuing until one subject experiences ≥ Grade 2 drug related toxicity (based on National Cancer Institute-Common Terminology Criteria for Adverse Events, Version 4 (NCI-CTCAE v4 [NCI-CTCAE, 2010]) or dose-limiting toxicity (DLT, see Section 4.2.4). The accelerated dose titration scheme is described in Table 1. A single dose (Day 1) will be given to subjects in each cohort with the collection of blood samples for PK analysis at timed intervals. Once the final PK sample for Day 1 is obtained, subjects may begin repeat dosing on Day 3. The dose for Dose Level 2 and subsequent cohorts will be based on the pharmacokinetics (PK) and safety analysis of the previous cohort. Inter-subject variability in exposure and toxicity will also be considered when deciding on actual doses administered during dose-escalation. Dose escalation will occur according to the procedures outlined in Table 1.

A sufficient number of subjects will be enrolled in each cohort to ensure that data from at least one subject that has completed a full treatment cycle (4 weeks) of dosing is available prior to defining a new dose and starting the next cohort. The dose-escalation decision and rationale for the subsequent cohort(s) will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

At the first occurrence of a DLT (refer to Section 4.2.4) or any Grade 2 toxicity (based on NCI-CTCAE v4) (with the exception of Grade 2 alopecia, nausea, vomiting, diarrhea, hemoglobin, lymphopenia, taste changes or alkaline phosphatase in the presence of bony metastases) during the first 4 weeks, the Accelerated Dose Titration procedure will be terminated. Once a DLT occurs, the ongoing cohort will be expanded up to 6 subjects and dose-escalation will continue following the 3 + 3 Dose-Escalation guidelines.

Table 1 Accelerated Dose Titration Procedures

Dose Level	Toxicity	Dose Escalation
Accelerated Dose Titration Phase		
Dose Level -1		Lower doses may be explored if DLTs or significant toxicities are observed at Dose Level 1.
Dose Level 1		Starting Dose: 3 mg daily
Subsequent Dose Levels	No subjects with either a ≥ Grade 2 toxicity or a DLT in first 4 weeks of treatment	Escalate to next dose level with an increase of ≤ 100%[a]
End of Accelerated Dose Titration Phase	One or more subjects with a ≥ Grade 2 toxicity or a DLT in first 4 weeks of treatment	Begin 3+3 dose-escalation phase

[a]: Dose levels in Section 4.2.1 are suggestions; the final determination of the next dose level will be made at the dose escalation meeting in concert with the Investigators, GSK Medical monitor, and representatives from Safety, Statistics, and Clinical Pharmacology. The final dose escalation decision will depend on all factors, as described in Section 11.2.1.

4.2.3. 3 + 3 Dose Escalation

Two additional subjects will be enrolled to the dose level at which accelerated dose titration ends, for a total of at least 3 subjects at that dose level. If no DLTs are observed in any of the 3 subjects, then dosing will proceed to the next higher dose level (≤2 fold increase in dose); however, if termination of accelerated dose titration is triggered by a DLT, then 5 additional subjects will be enrolled at that dose level. Subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the MTD in multiple subjects. Dose escalation decisions will be made as outlined in Table 2 Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. Intra-subject dose escalation may be considered as described in Section 4.2.7. Subjects should not be enrolled at a higher dose level until at least 3 subjects in the previous dose cohort complete 4 weeks of treatment.

Dose-limiting toxicity (DLT) is based on any observed toxicity in the first 4 weeks. If 1 of 3 subjects experiences a DLT at a particular dose level, 3 additional subjects will be enrolled at that dose level. If 2 or more subjects experience a DLT at a particular dose level, a lower (or intermediate) dose level may be explored to better define the maximum tolerated dose (MTD).

If 2 or more DLTs in 6 subjects are observed at any dose level, the MTD will have been exceeded (Table 2).

Table 2 3 + 3 Dose Escalation Design

Number of Subjects with DLT in a Cohort	Action
0 out of 3 subjects	Escalate to next dose level with an increase of ≤ 100%[a] • If two or more subjects have the same ≥ Grade 2 drug-related adverse event, consider a <2-fold increase[a] taking into consideration the safety profile and dose-exposure relationship
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to the next dose level with an increase of ≤50%[a]
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to a total of 12 subjects
1 or more out of 6 subjects at the highest dose level below the MTD	The dose is considered the recommended Phase 2 dose (RP2D). At least 6 subjects must be evaluated at the RP2D dose.

[a]: Dose levels in Section 4.2.1 are suggestions; the final determination of the next dose level will be made at the dose escalation meeting in concert with the Investigators, GSK Medical monitor, and representatives from Safety, Statistics, and Clinical Pharmacology. The final dose escalation decision will depend on all factors, as described in Section 11.2.1.

The RP2D will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile, and available PD data generated from all subjects. If necessary alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

4.2.4. Dose-Limiting Toxicity

An event is considered to be a dose-limiting toxicity (DLT) if the event is attributed (definitely, probably or possibly) to the study treatment during the first 4 weeks of treatment and meets the criteria described in

Table 3, as graded when applicable by the NCI-CTCAE v4.

Subjects who are unable to receive at least 75% of the scheduled doses during the 4-week DLT evaluation period will be replaced in the cohort unless the reason for the delay or discontinuation was due to a DLT.

Table 3 Dose –Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 for ≥5 days) • Febrile neutropenia (as defined by NCI-CTCAE v4 [concurrent Grade 4 neutropenia and fever >38.3°C]) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000/mm^3)
Non-hematologic	• ALT >3x upper limit of normal (ULN) + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin < 2xULN but with hepatitis symptoms or rash (See Section 5.4.1 for Liver

Toxicity	DLT Definition
	Stopping Criteria) • Grade 3 nausea, vomiting or diarrhea that does not improve within 24h despite appropriate supportive treatment(s) • Grade 4 nausea, vomiting, or diarrhea • Grade 3 hypertensiona (uncontrolled despite addition of up to 2 antihypertensive medications) • Grade 4 hypertension • Grade 3 or greater clinically significant non-hematologic toxicity (including QTcF) per NCI-CTCAE, v4 except toxicities listed in Section 4.2.5 • Grade 2 troponin elevation (central laboratory >ULN), measured on two separate occasions within 48 hours in order to confirm elevation and with other clinical signs, symptoms, laboratory tests consistent with cardiac toxicityb.
Other	• Any toxicity resulting in a dose delay of >14 days of the intended next dose • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

Toxicity Grading based on NCI-CTCAE v4

a. Grade 3 hypertension adequately controlled by antihypertensive medication(s) is not considered to be a DLT.

b. In the event a troponin (central laboratory assessment) is not performed or a laboratory error occurs, considerations for a DLT criterion will involve review of two separate local troponin (I or T) assays done within 48 hours at a local investigator site. Troponin I or T elevations greater than the upper limit of normal, and > 10% coefficient of variance (CV) for that assay will be considered as a grade 2 elevation.

4.2.5. Non-Limiting Toxicities

The following toxicities have been deemed to be non-serious for the purposes of this study. These toxicities will not be taken into account for dose escalation decisions unless, in the opinion of the investigator and the GSK Medical Monitor, they represent a dose-limiting toxicity. For all other toxicities and their management, see Section 14.7.

- Grade 3 or less:
  - Fatigue
  - Rash
  - Mucositis
  - Asthenia
  - Alopecia
- Electrolyte imbalance or other laboratory abnormalities controlled within 24h

4.2.6. Alteration of Schedule

Alterations may be made to the schedule of administration and/or PK/PD sampling schedule based on the results of emerging PK and safety data.

Schedules that incorporate a recovery period may be explored (e.g., 2 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using 3 + 3 dose escalation.

Schedules that use a shorter recovery period, e.g., twice daily (BID) dosing, may also be explored. This approach will be considered if the safety, PK, and emerging PD data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule. If a shorter recovery period is used, the initial dose level will be ≤50% of the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using the 3 + 3 dose escalation. Alternative schedules with intense supportive care may also be explored.

The dosing schedule may also be adjusted to expand a prior dose cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

4.2.7. Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced any Grade 2 or higher drug related toxicity prior to dose escalation in the accelerated dose escalation phase or a DLT in the 3+3 dose escalation phase and contingent upon the following:

Additional subject(s) have been enrolled at a higher dose in the dose escalation phase and at least one subject has completed 4 weeks of dosing on that regimen without a DLT; and after review of all safety data and approval by a GSK Medical Monitor, a subject on a lower dose level may be increased up to the highest dose level tested. In this case the subject may begin dosing at the higher dose level as it will have already been demonstrated to be tolerable.

Subjects approved for intra-subject dose escalation will require additional limited PK sampling at the higher dose, as determined by GSK Clinical Pharmacology. Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

4.3. Type and Number of Subjects

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) of GSK2820151 for further study. It is estimated 30 to 50 evaluable subjects will be enrolled.

Approximately 30 to 50 subjects with will be enrolled in the study. The study population will be adults, with advanced or recurrent solid malignancy, who either:

- refuse standard therapy,
- are not candidates for standard therapy,
- have a disease for which no non-investigational therapy exists, OR
- have progressed on prior therapy (up to three lines of prior cytotoxic agents are permitted).

If a subject discontinues the study before completing Week 4 due to reasons other than toxicity, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator to ensure an adequate population for DLT and MTD evaluations.

4.4. Design Justification

Given the high unmet medical need of relapsed/refractory, advanced solid tumors, a conventional Phase I study (201893) is proposed. The study comprises an accelerated dose titration to determine a MTD. While preliminary efficacy data will be collected as part of the course of the study, it will not be a primary endpoint. Overall, the aim of the study is to identify a RP2D for future evaluation of GSK2820151.

While dose escalation and subject enrollment will utilize a conventional 3+3 approach, determination of the particular dose to be tested in each cohort will utilize all available information, including input from the N-CRM model. The updated model from the N-CRM analysis after each subject is evaluated will give more information about the expected DLT rate at each dose level and assist in the dose-escalation decision making process.

4.5. Dose Justification

4.5.1. Human Pharmacokinetic Extrapolation

Human pharmacokinetics was predicted based on three species (mouse, rat and dog) using different allometric extrapolation. Whole blood human clearance predicted from mean of allometry was 6.5 ml/min/kg (~30% hepatic blood flow). Volume of distribution at steady state was predicted to be 2.8 L/kg with a moderate half life of ~5hr. Bioavailability is predicted to be ~69%.

4.5.2. Starting Dose

The 28 day toxicology studies were conducted using the freebase of GSK2820151 whereas the mesylate salt of GSK2820151 will be used on this clinical study. Comparison of systemic exposure between the freebase and mesylate versions of GSK2820151 at the same dose level (corrected for form) showed that systemic exposure was comparable in the rat, but the mesylate salt resulted in 2-4.6 fold higher exposure in the dog. Taking into account the difference in systemic exposure for the dog (and using the more conservative approach of 4.6 fold difference), the dose level required to achieve equivalent systemic exposure has been adjusted (i.e. highest non-severely toxic dose (HNSTD) freebase of 5 mg/kg is equivalent to HNSTD mesylate of 1.09 mg/kg.).

Three approaches have been considered to establish the starting dose for GSK2820151.

- One tenth of the rat severely toxic dose in 10% of the animals (STD10)

  For GSK2820151, the STD10 was defined as 3 mg/kg in the rat following International Conference on Harmonization (ICH) S9 guidelines. 1/10 rat STD10 is 1.8 mg/m^2; this dose is not severely toxic to dogs and translates to a starting dose in man of 3 mg, assuming a 70 kg adult and adult surface area of 1.7 m^2.

- One sixth of the dog HNSTD

  For GSK2820151, the dog HNSTD is defined as 1.09 mg/kg. 1/6 dog HNSTD is 3.63 mg/m^2 which translates to a starting dose in man of 6 mg, assuming a 70 kg adult and adult surface area of 1.7 m^2.

- The dose predicted to deliver a minimum anticipated biologicaleffect t level minimum anticipated biological effect level, (MABEL) dose.

The potential therapeutic effect of GSK2820151 was evaluated at single oral daily doses of 10 mg/kg (30 mg/m^2) and 30 mg/kg (90 mg/m^2) in OPM-2 transgenic non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mouse xenograft model of multiple myeloma; 25 mg/kg (75 mg/m^2) daily and 50 mg/kg (150 mg/m^2) every other day in NCI-H526 SCLC xenograft model and 30 mg/kg (90 mg/m^2) daily in NMC xenograft model. GSK2820151 was efficacious at 30 mg/kg in both studies and showed partial efficacy at 10 mg/kg dose in OPM-2 xenograft model. 25 mg/kg dose showed ~24% reduction in tumor growth while 50 mg/kg showed ~54% reduction in tumor volume. The mouse MABEL dose of 10 mg/kg (30 mg/m^2) would translate to a dose in

human of 125 mg using human equivalent dose calculation. Taking a conservative approach, the starting dose will be 3 mg.

The predicted human exposure at 3 mg is area under the curve from zero to 24 hours (AUC_{0-24}) = 78.8 ng/h/mL and is approximately 6-fold lower than the exposure at the dog NOAEL / HNSTD and approximately 9- and 47-fold lower than the rat no observed adverse effect level (NOAEL) and STD10 exposures, respectively.

4.6. Benefit:Risk Assessment

Summaries of findings from the non-clinical studies conducted with GSK2820151 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2014N208278_00]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiovascular	**QT Prolongation** Observed after single dose in dogs (100 mg/kg; up to 34 msec and up to 48hr post dosing) and after repeat dosing in dogs (≥ 30 mg/kg/day from Day 3; up to 21 msec). Mechanism is unclear (no clear link to human *ether-à-go-go*-related gene [hERG] binding); QT prolongation observed at unbound *in vivo* drug concentrations approximately 100-fold lower than in vitro hERG inhibition (IC_{50}). Increased number of arrhythmias observed in 1 of 3 dogs which had highest drug exposure after a single dose of 100mg/kg (10x the dog 28 day MTD). **Blood Pressure (BP)** Increases in blood pressure (mean, systolic & diastolic; systolic affected more than diastolic) observed following single dose in dogs. Mean up to 38 mmHg and up to 42 hours post dosing. **Heart Rate** Increased heart rate after a single and repeat	Informed consent form (ICF) includes the risk of (fatal) arrhythmias and the risk of myocardial infarction Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 7.1.2). Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK], creatine kinase-MB [CK-MB], and troponins [local laboratory monitoring for troponin I or T based on availability and troponin T at central laboratory]), cardiac monitoring (ECGs, Holter monitoring and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management of cardiac events. All subjects will receive their first dose of study medication (Week 1 Day 1) in the hospital with telemetry monitoring for the first 48 hours of dosing. Throughout the protocol, the role of intensive cardiac monitoring will be re-evaluated in an ongoing fashion with the aim of re-evaluating cardiac risk mitigation strategy while maintaining subject safety.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	doses of 100 mg/kg in dogs (single dog up to 24 beats per minute (BPM) between 9 and 19 hours post dosing after a single dose and single dog up to 94 bpmafter repeat dosing.). **Cardiac Biomarkers** Reversible increases in serum cardiac troponin I (cTnI) levels were observed in male rats (up to 3.3X) at 10 mg/kg/day for 28 days. Increased NT pro-ANP (up to 2.1X) in female rats given ≥1 mg/kg/day for 28 days; no recovery after up to 5 weeks off dose period. No histologic lesions in the heart on 28 day studies.	
Gastrointestinal (GI) (Dose-limiting toxicity in rats and dogs)	Gastrointestinal effects were the dose limiting toxicity in both rats and dogs at doses ≥6 and 20 mg/kg/day respectively. Clinical presentation included altered feces, reduced food consumption and reduction in body weight; microscopic changes observed at doses ≥6 and 20 mg/kg/day in rats and dogs respectively included erosion / ulceration / haemorrhage / mucosal epithelium degeneration/regeneration, villous atrophy, inflammatory cell infiltration and mild cecal lamina propria fibrosis (dogs only). Signs of recovery immediately after cessation of	ICF includes the risk of gastrointestinal effects. Protocol includes medical history, physical examination (including weight) and clinical laboratory assessments to assess toxicity in the GI tract. Subjects with a history of gastrointestinal bleeding in the past 6 months (Section 5.2) or active bleeding will be excluded. Protocol also includes specific dose adjustment/stopping safety criteria for diarrhea and mucositis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	dosing; no microscopic findings after up to 5 weeks off dose.	
Lymphoid/Hematologic	Lymphoid / hematologic toxicity was observed in rats and dogs at ≥3 and ≥5 mg/kg/day respectively. The effects manifested as hypocellularity in bone marrow of rats and dogs and reduced cellularity of the thymus, lymph nodes and spleen in rats accompanied by microscopic evidence of increased red cell turnover. Peripheral effects included reductions in red blood cells, platelets and increases in neutrophils (in response to GI toxicity). Effects on reticulocyte counts were variable. Reversible increased activated thromboplastin (APTT) time in rats and dogs (≥1 mg/kg/day and 20 mg/kg/day respectively). A mild decrease in APTT in female rats at 3 mg/kg/day. Reversible increases in fibrinogen (1.51X) in dogs dosed at 20 mg/kg/day. Regenerative response in blood cell parameters and microscopic observation of extramedullary haemopoiesis was evident after up to 5 weeks off-dose.	ICF includes the risk of lymphoid / hematologic toxicity. Protocol includes laboratory assessments (complete blood count [CBC] and coagulation factors [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], exclusion criteria if there is evidence of clinically significant bleeding episodes, monitoring for bruising/infection and dose stopping/modifications criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Reproductive	Testicular degeneration was observed in both rats (10 mg/kg) and dogs as well as disorganised spermatogenesis in dog at ≥5 mg/kg. Secondary changes were evident in epididymides (hypospermia, degenerate cells, atrophy, vacuolation). No evidence of reversibility within 3 week off dose period. Reversible reduced prostate weight (rat and dog) & decreased secretory content in prostate (rat ≥ 3 mg/kg/day) and seminal vesicles (rat 10 mg/kg/day) were observed.	ICF includes the risk of damage to reproductive organs such as testes or ovaries. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and complete) for male subjects. ICF includes the potential risk of reproductive effects.
Liver and Gallbladder Effects Hepatobiliary	Dog: Minimal gallbladder vacuolization and minimal vacuolization of biliary epithelium in dogs dosed at 20 mg/kg/day. Effects were reversible. Rat: Reversible decreased inflammatory cell infiltrate in animals dosed at ≥ 3 mg/kg/day.	ICF includes the risk of hepatic/gallbladder effects. Protocol includes hepatic eligibility criteria, laboratory assessments during the study, and dose stopping/modifications criteria for the management of hepatic events.
Lung Effects	Minimal to mild prominent (foamy) alveolar macrophages were observed in rats administered ≥ 1 mg/kg/day. Effects were reversible. The clinical consequences of this finding are unknown.	ICF includes the risk of lung effects. Protocol includes pulmonary function assessments as appropriate (subjects with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage, chest radiation) chest x-ray at baseline and dose stopping/modifications criteria

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		for pneumonitis.
Teeth	Minimal to mild changes related to dentin formation in continuously growing incisors of rats dosed at ≥ 3 mg/kg/day. Marginally increased incidence and/or severity after off dose period. No changes observed in molar teeth.	Due to the differences between rodents and human, it is unlikely that these effects of teeth will affect human adults.

4.6.2. Benefit Assessment

Study 201893 is an open-label, dose escalation study and the first study of this agent to be conducted in subjects with relapsed and/or refractory advanced solid malignancies for which no standard therapies are available. GSK2820151 has promising preclinical activity in cell lines; however it is unknown whether GSK2820151 will have clinical efficacy in subjects with solid tumors. As such, any potential beneficial effect for an individual subject attributable to GSK2820151 is unknown. Data obtained in Study 201893 may assist in progressing the knowledge base on advanced malignancies and their treatment, or help identify individuals more likely to benefit or have side effects from GSK2820151.

4.6.3. Overall Benefit:Risk Conclusion

Current data from preclinical development indicate GSK2820151 inhibits the BET family of BRD proteins, and that this inhibition may have clinical utility in the treatment of various tumors. Taking into account the measures taken to minimise risk to subjects participating in the Phase I clinical trials, the potential risks identified in association with GSK2820151 are justified by the anticipated benefits that may be afforded to subjects with relapsed/refractory advanced solid malignancies with otherwise limited therapeutic options.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the GSK2820151 Investigator Brochure [GlaxoSmithKline Document Number 2014N208278_00]. Approximately 30-50 subjects with relapsed or advanced solid malignancies will be enrolled. All subjects must have failed refused or otherwise be ineligible for standard therapy, failed up to three lines of cytotoxic therapy, or have a tumor for which there is no standard therapy, prior to consideration for study. The total number of subjects required will depend upon the number of escalation steps required to reach a MTD.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and enrolled

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Written informed consent provided

2. Males and females 18 years old and greater
3. Diagnosis of advanced or recurrent solid malignancy. At time of enrollment, subjects either:
   - refuse standard therapy,
   - are not candidates for standard therapy,
   - have a disease for which no non-investigational therapy exists, OR
   - have progressed on prior therapy (up to three lines of prior cytotoxic agents are permitted).
4. Subjects with solid tumors, with the exception of castration-resistant prostate cancer (CRPC), must demonstrate measurable disease, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
5. All prior treatment- related toxicities must be NCI-CTCAE v4 ≤ Grade 1 (except alopecia [permissible at any Grade] and peripheral neuropathy [which must be ≤ Grade 2]) at the time of treatment allocation.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 1 (See Appendix 2 for definitions).
7. Adequate organ function as defined in Table 4.

Table 4 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 9 g/dL (subjects that required transfusion or growth factor need to demonstrate stable hemoglobin for 7 days of 9 g/dL)
Platelets	≥ 100 X 10^9/L
PT/INR and PTT	≤ 1.5 X upper limit of normal (ULN)
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤ 1.5 x X ULN (isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome)
Alanine aminotransferase (ALT)	≤2.5 × ULN OR <5 x ULN is acceptable for subjects with documented liver metastases/tumor infiltration
Renal	
Creatinine OR Creatinine clearance [either directly measured or calculated by Cockcroft-Gault formula[b]]	≤1.5 X ULN ≥ 40 mL/min
Cardiac	
Ejection fraction	≥ 50% by echocardiogram or multigated acquisition scan (MUGA)
Troponin (T)	≤ ULN
Potassium	≥Lower limit of normal (LLN) and ≤ULN
Magnesium	≥LLN[a]

a. Magnesium supplementation is permitted, as required, to maintain a serum magnerium concentrations ≥ LNN
b. Cockcroft and Gault Method for Calculated Creatinine Clearance is provided in Appendix 9.

8. Able to swallow and retain orally administered medication.
9. A female subject is eligible to participate if she is of:

   - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation, hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, hysterectomy, or documented bilateral tubal oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) >40 U/ml and estradiol <40 pg/ml (<140 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status,

they can resume use of HRT during the study without use of a contraceptive method.

- Child-bearing potential and agrees to use one of the contraception methods (described in Section 7.3) for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until at least 4 weeks after the last dose of study medication.
- Negative serum pregnancy test ≤ 7 days prior to first study drug dose.
- Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 5 half-lives of GSK2820151 or at least 28 days (whichever is longer) following the last dose of study treatment.

10. Male subjects with female partners of child bearing potential must agree to use one of the methods of contraception specified (see Section 7.4). This method must be used from the time of the first dose of study medication until at least 16 weeks after the last dose of study medication.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Primary malignancy of the central nervous system or malignancies related to human immunodeficiency virus (HIV) or solid organ transplant.
2. More than three prior lines of cytotoxic therapy.
3. Recent prior therapy, defined as follows:
    a. Any investigational or Food and Drug Administration (FDA)-approved anti-cancer drug within 14 days or 5 half-lives, whichever is longer, prior to the first dose of GSK2820151. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK2820151. Prior therapy with monoclonal antibodies is permitted so long as 14 days have elapsed since therapy and all therapy-related toxicity has resolved to Grade 1 or less. Note that an investigational drug is defined as a drug without an approved oncologic indication
    b. Any radiotherapy within 14 days or major surgery within 28 days prior to the first dose of GSK2820151.
    c. Anti-androgen therapies for prostate cancer, such as bicalutamide, must be stopped 4 weeks prior to enrollment. Second-line hormone therapies such as enzalutamide, abiraterone, or orteronel should be stopped 2 weeks prior to enrolment. Subjects with prostate cancer should remain on luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

d. In addition, any therapy-related toxicity must have resolved to Grade 1 or less, with the exception of alopecia (acceptable at any Grade) and peripheral neuropathy (which must be Grade 2 or less prior to enrollment).

4. Therapeutic anticoagulation (e.g., warfarin, heparin) must be discontinued and coagulation parameters must be normalized prior to the first dose of GSK2820151. Low dose (prophylactic) low molecular weight heparin (LMWH) is permitted. In addition, INR must be monitored in accordance with local institutional practices.
5. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK2820151 (see Section 7.1.2 for the list of medications).
6. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.
7. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

NOTE: Subjects previously treated for these conditions that have had stable central nervous system (CNS) disease (verified with consecutive imaging studies) for >1months, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 1 month prior to study Day 1 are permitted. Stability of brain metastases must be confirmed with imaging. Subject treated with gamma knife therapy can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications/stable. In addition, subjects treated or currently taking enzyme-inducing anticonvulsant (EIAC) are allowed on study.

8. Cardiac abnormalities as evidenced by any of the following:
   - History of or current "untreated" clinically significant uncontrolled arrhythmias.
   - Clinically significant conduction abnormalities or arrhythmias
   - Presence of cardiac pacemaker
   - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
   - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing antithrombotic therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.
9. Any of the following electrocardiogram (ECG) findings:
   - Baseline Corrected QT (Fridericia's formula) interval (QTcF) ≥450 msec

NOTE: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.

10. Any of the following liver findings:
    - ALT >2.5xULN
    - ALT > 5xULN with liver metastases/tumor infiltration
    - Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    - Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).

NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice or cirrhosis

11. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. History of known HIV infection.

NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA polymerase chain reaction (PCR) is obtained.

12. Any serious known immediate or delayed hypersensitivity reaction(s) to GSK2820151 or idiosyncrasy to drugs chemically related to the investigational drug.
13. Hemoptysis > 1 teaspoon in 24 hours within the last 28 days.
14. History of major gastrointestinal bleeding within the last 6 months.
15. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently enrolled. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry, hematologic/non-hematologic toxicity, QTc prolongation, or left ventricular ejection fraction (LVEF)/valvular dysfunction as defined in Section 5.4.1 through Section 5.4.5. After

disease progression, subjects may be allowed to continue treatment with study drug if the Investigator strongly believes, and the GSK Medical Monitor concurs, that the subject could continue to receive benefit (for example in cases of an isolated new lesion, with the majority of the disease still under control).

In addition study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in Time and Events Tables (see Section 8.1).

All subjects who permanently discontinue study treatment without disease progression will be followed for progression according to the protocol schedule until:

- new anti-cancer therapy is initiated
- progression
- death, or
- subject has been followed for 2 years after stopping treatment.

All subjects who permanently discontinue study treatment will be followed for survival and new anti-cancer therapy (including radiotherapy) every 6 months until death, termination of the study by the sponsor, or until the subject has been followed for 2 years. If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

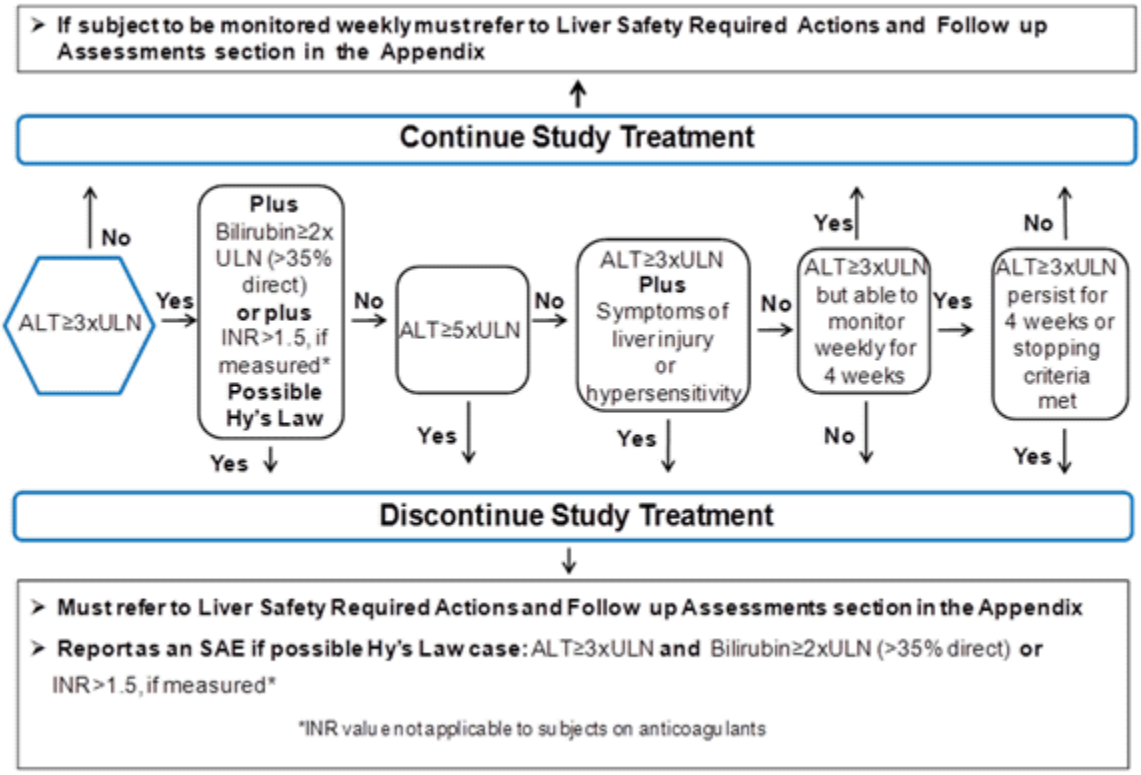
A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

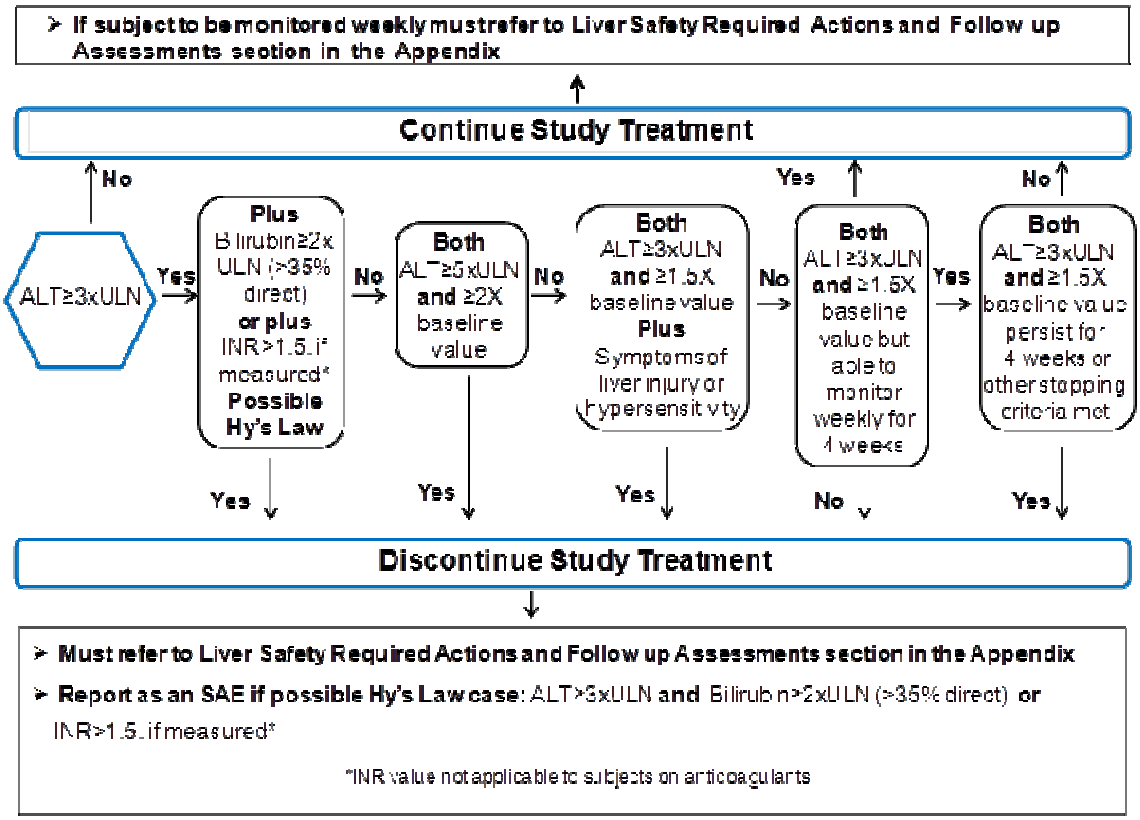
See Figure 3 and Figure 4 for liver stopping criteria for subjects without and with liver metastases, respectively.

Figure 3 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

Figure 4 **Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN**



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

5.4.1.1. Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted
- Ethics and/or institutional review board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 4 for full guidance.

5.4.2. QTc Stopping Criteria

If a subject meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QTcF interval ≥ 500 msec OR interval increase from baseline ≥ 60 msec: GSK2820151 will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the GSK Medical Monitor, as well as the GSK medical governance. In this situation, rechallenge may be permitted (see Appendix 7 for rechallenge guidelines).

NOTE: QT interval duration criteria should be based on the average QTc value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment discontinued.

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

- For eligibility and withdrawal, QTcF will be used for all subjects.
- For purposes of data analysis, QTcF will be used.

5.4.3. LVEF Stopping Criteria

Echocardiography must be performed at Screening, Week 5 Day 1, Week 9 Day 1, and every 8 week thereafter and at the post-treatment follow-up visit as outlined in the Time and Events Table (Section 8.1). Subjects who have an asymptomatic, absolute decrease of >10% in left ventricular ejection fraction (LVEF) compared with baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue GSK2820151 and have a repeat evaluation of LVEF within 1 week. Echocardiogram (ECHO) should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation with and approval from the GSK Medical Monitor, the subject may be restarted on GSK2820151 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK2820151 should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Subjects with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue treatment with GSK2820151. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >institutional LLN and symptom resolution) within 4 weeks, treatment with GSK2820151 may be restarted at a reduced dose in consultation with the GSK Medical Monitor.

Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the Study Reference Manual (SRM).

5.4.4. Valvular Toxicity Stopping Criteria

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (ECHO) (Grade 2 mitral/tricuspid/aortic valvular toxicity per NCI-CTCAE v4) should temporarily discontinue GSK2820151 and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation with and approval from the GSK Medical Monitor, the subject may be restarted on GSK2820151 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK2820151. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK2820151. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart GSK2820151 at a reduced dose after consultation with and approval from the GSK Medical Monitor.

ECHO must be performed at baseline and at the final study visit. Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the Study Reference Manual (SRM).

5.4.5. Other Stopping Criteria

All subjects will require a chest X-ray and pulmonary function testing at screening, as defined in the Time and Events table. Subjects with clinical concern for pneumonitis will be evaluated per institutional practice with input from the GSK medical monitor. For management of suspected pneumonitis, including criteria for dose reduction and discontinuation of therapy, see Appendix 7.

To monitor for thrombocytopenia, CBCs will be drawn twice weekly for the first three weeks of study, weekly for the next two weeks, and then every other week, as described in the Time and Events table. Subjects who develop Grade 2 or greater thrombocytopenia may be monitored more frequently, as clinically indicated. Please see Appendix 7 for suggested management of thrombocytopenia.

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics). Deaths, SAEs, and Grade 3/4 adverse events will be carefully evaluated for the possibility of causality.

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, and/or if deaths related to study drug are observed, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded. The final determination will be made by the Sponsor and investigators.

5.5. Subject and Study Completion

A completed subject is one who has discontinued study treatment for reasons listed in Section 5.4 and completed a post-treatment follow-up visit or has died while receiving study treatment.

A subject will be considered to have completed the study 2 years after the last treatment or if the subject dies or is still in follow-up at the time the study is closed or terminated, whichever is sooner. Document the cause of death in the eCRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. GSK2820151

The term 'study treatment' is used throughout the protocol to describe the administration of GSK2820151.

	Study Treatment
Product name:	GSK2820151
Formulation description:	GSK2820151 capsules contain 1 mg, 5 mg, 10 mg, 50 mg, or 100 mg of GSK2820151 as free base equivalent
Dosage form:	Capsule
Unit dose strength(s)/Dosage level(s):	1 mg, 5 mg, 10 mg, 50 mg, and 100 mg
Route of Administration	Oral
Dosing instructions:	The dosing regimen is detailed in Table 7 and is designed to permit collection of detailed safety and PK data. • Week 1: Once daily on days 1, 3, 4, and 5 • Week 2: Once daily on days 1, 2, 3, 4, 5 • Weeks 3 and beyond: Once daily continuously GSK2820151 is to be administered orally, once daily, at approximately the same time of day, with no food or antacids for 1 h before and 2 h after each dose
Physical description:	1 mg: Pink, Size 1 capsule 5 mg: Green, Size 1 capsule 10 mg: Swedish Orange, Size 1 capsule 50 mg: White Opaque, Size 0 capsule 100 mg: Blue Opaque, Size 0 capsule

6.2. Treatment Assignment

Subjects will be assigned to receive GSK2820151 in an open-label fashion. There will be no placebo arm.

6.3. Packaging and Labeling

GSK2820151 will be provided to the sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated)

area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor or GSK study contact.

Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK2820151.

6.5. Compliance with Study Treatment Administration

At each visit, an evaluation of subject compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant subjects into compliance.

Compliance with GSK2820151 will be assessed through querying the subject during the site visits and documented in the source documents and CRF.

A record of the number of GSK2820151 tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.6. Treatment of Study Treatment Overdose

For this study, any dose of GSK2820151 greater than the protocol-specified dose within a 24 hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator (or treating physician) should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2820151 can no longer be detected systemically (at least 28 days for GSK2820151)
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.7. Treatment after the End of the Study

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) therapy at the discretion of the treating physician. New therapy should be documented on the CRF. Every effort should be made to complete the required withdrawal and follow up evaluations prior to initiating further therapy or dosing of an investigational agent (see Section 8.1 for follow-up assessments and procedures).

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

7. MEDICATION, LIFESTYLE, AND DIETARY RESTRICTIONS

7.1. Concomitant Medications and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the Screening Visit until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, route of administration, dose and frequency of dosing, along with start and stop dates of administration should be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

7.1.1. Permitted Medications and Non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with erythropoietin, antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Colony-stimulating factors like filgrastim and pegfilgrastim may be used in cycles 2 and beyond as clinically indicated.The only caveat is that subjects should not receive those medications listed as prohibited in Section 7.1.2.1.

Bisphosphonates will be allowed if subjects have been on a stable dose for at least three months prior to receiving the first dose of GSK2820151.

7.1.2. Prohibited Medications and Non-Drug Therapies

7.1.2.1. Prohibited Medications

The use of certain medications and illicit drugs within 5 half-lives or 28 days (if the drug is a potential enzyme inducer) prior to the first dose of study medication (and for the duration of the study) will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study treatment(s) is held, the GSK Medical Monitor can approve such use.

Anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc.) are PROHIBITED from seven days prior to the first dose of study drug through completion of the Final Study Visit. Low dose (prophylactic) anticoagulants are permitted provided that the subject's PT/PTT values meet entry criteria.

Subjects should not receive other anti-cancer therapy [including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormonal therapy (other than leuprolide or other LHRH agonists/antagonists), surgery or tumor embolization] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. Note, palliative radiation and/or surgical intervention may be permitted (for example to address pain management) and should be discussed with the GSK medical monitor prior to invention to determine appropriate dosing and schedule.

Co-administration of the following medications are **PROHIBITED** for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of **amiodarone** which is prohibited beginning **6 months** prior to Screening through discontinuation from the study. [However, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines]). These medications include (but are not limited to):

Table 5 Drugs with a Risk of Torsades de Pointes that are Prohibited

Amiodarone	Dronedarone	Moxifloxacin
Anagrelide	Droperidol	Pentamidine
Azithromycin	Erythromycin	Pimozide
Chloroquine	Escitalopram	Procainamide
Chlorpromazine	Flecainide	Quinidine
Citalopram	Halofantrine	Sevoflurane
Clarithromycin	Haloperidol	Sotalol
Cocaine	Ibutilide	Thioridazine
Disopyramide	Levofloxacin	
Dofetilide	Methadone	

Data Source: crediblemeds.org revision date 26 September 2014

At time of screening, if a subject is currently receiving any of the listed prohibited medications/substances, the medication or substance must be discontinued for a period of 5 half lives (or at least 14 days, whichever is longer) prior to the administration of the first dose of study drug in order for the subject to meet study eligibility.

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (up to a maximum dose of 0.25 mg daily) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class.

7.1.2.2. Prohibited Non-Drug Therapies

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the transition visit through the post-study follow-up visit.

NOTE: Subjects may receive focal palliative radiation treatment during this study. Any proposed radiation therapy must be approved by the investigator and the GSK Medical Monitor prior to initiation.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit.

Herbal products include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto , ginseng.

The investigator should contact a GSK Medical Monitor before initiating treatment with any herbal preparation including marijuana.

7.1.3. Cautionary Medications

Co-administration of GSK2820151 and the following medications **requires EXTREME CAUTION** beginning **14** days prior to the first dose of study drug until discontinuation from the study, due to an increased risk of Torsades de Pointes. These medications include (but are not limited to):

Table 6 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Alfuzosin	Iloperidone	Quetiapine
Apomorphine	Isradipine	Ranolazine
Aripiprazole	Lithium	Rilpivirine
Atazanavir	Mifepristone	Risperidone
Bedaquiline	Mirabegron	Saquinavir
Clozapine	Mirtazapine	Tacrolimus
Dexmedetomidine	Moexipril/HCTZ	Telavancin
Dihydroartemisinin+piperaquine	Nicardipine	Telithromycin
Dolasetron	Norfloxacin	Tetrabenazine
Famotidine	Ofloxacin	Tizanidine
Felbamate	Olanzapine	Tolterodine
Fingolimod	Oxytocin	Vardenafil
Foscarnet	Paliperidone	Venlafaxine
Fosphenytoin	Pasireotide	Ziprasidone
Gemifloxacin	Perflutren lipid microspheres	
Granisetron	Promethazine	

Data Source: crediblemeds.org revision date 26 September 2014

Note: This list is not exhaustive. Drugs and/or drug names not available/used in the US have been omitted

After starting cautionary medications such as in Table 6, it is recommended that ECGs are implemented daily until the steady state of the new medication is reached. If there are ECG abnormalities, implement additional cardiotoxicity monitoring as addressed Appendix 7.

There is a low potential for GSK2820151 to induce or inhibit cytochrome P450 (CYP) enzymes. GSK2820151 has been demonstrated to inhibit Breast Cancer Resistance Protein (BCRP [IC_{50}=3.6 μM]) and thus may alter the metabolism of medications that are substrates of BCRP. These medications include HMG-CoA reductase inhibitors (statins) as well as ciprofloxacin and other fluoroquinolones (though not levofloxacin).

Furthermore, GSK2820151 inhibits P-glycoprotein (PgP) at concentrations ≥ 100 μM. PgP substrates include medications such as statins and digoxin, which may have a narrow therapeutic index. While co-administration of these agents with GSK2820151 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

GSK2820151 may also interact with organic anion transporter 3 (OAT3). Substrates of OAT3 include agents such as Penicillin G, indomethacin, and ciprofloxacin. While co-administration of these agents with GSK2820151 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

7.2. Dietary Restrictions

GSK2820151 will be administered under fasting conditions, with no food or antacids for 1 h before and 2 h after each dose. Requirements for fasting before and after dosing may be modified based on available pharmacokinetics (PK), pharmacodynamics (PD) and safety data. Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted. Subjects will be instructed to record the time and date of study treatments and meals in relation to dosing in the supplied GSK dosing diary.

Subjects will abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final PK and or PD sample during each serial PK sampling day (e.g., Days 1 and 18).

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment until the last dose of study drug.

On serial PK sampling days, subjects enrolled in the serial PK cohort should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.

7.3. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

Hormonal means of birth control such as oral contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

7.4. Male Subjects

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment and until 16 weeks after the last dose of study drug.

- Condom plus partner use of a highly effective contraceptive such as occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/film/cream/suppository), or intrauterine device. **OR**
- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 8.1

8.1. Time and Events Tables

Table 7 Time and Events

Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X	X	X			X	X	X	X	X			Daily									
Review subject diary	Diary not required when dosed in clinic.									X							X		X		X	X	X	X		
Safety																										
Pregnancy test/ testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X

Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X	X				X		X					X		X		X		X	X	X	X		X
Pain		X	X	X				X		X					X		X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test		X																								
Adverse events		*continuous from signing of informed consent*																								
Concomitant medications		*continuous from signing of informed consent*																								
Laboratory assessments: For details please see following tables																										
Tests		X	X	X				X		X					X		X		X		X	X	X	X	X	X
Cardiac Monitoring																										
Echocardiogram	Within 35 days of first dose	X																			X		X		X	X
12-lead ECGs (Triplicate)	Triplicate SCR ECGs within 35 days of first dose. For timing of triplicate ECGs on O days, see Table 9 and Table 10. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O	O	X		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X	X				X							X					X				X			
Telemetry	Start at least 60 min predose and for at least 48 h.		X	X																						

Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Efficacy																										
Cross-sectional (Computed tomography [CT] or magnetic resonance imaging [MRI]), functional (Positron emission tomography [PET]), or nuclear (bone scan) imaging	Appropriate imaging modality should be selected by the investigator depending on disease histology and location. SCR assessment within 2 weeks of first dose. Target lesions to be identified at SCR and followed. See Section 14.8.1 for guidelines.	X																					X		X	X
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see Table 9 and Table 10																										
PK and biomarker samples			X	X			X						X					X					X			
Samples for mRNA		X	X	X														X								X
LPS blood sample			X																							
PK Urine samples			X															X								
Pharmacogenomics (PGx)																										
PGx sample			X																							
FOLLOW-UP PHASE																										

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death.

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; O= For timing of triplicate ECGs on O days, see Table 9 and Table 10; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; W=week

Table 8 Time and Events: Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	W1			W2		W3	W4	W5	W7	W9	q4W	q8W	EOT
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP-9	W1D1, W1D2: local lab sample 3X/24h; central lab sample 1X/24h. Unscheduled collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X	X		X		X	X
Hematology		X	X		X	X	X	X[1]	X	X	X	X	X		X
Clinical chemistry		X	X		X	X	X	X	X	X	X	X	X		X
Pancreatic		X	X		X	X		X		X	X	X	X		X
Coagulation		X	X		X	X		X		X	X	X	X		X
Creatine phosphokinase		X	X		X	X		X		X	X	X	X		X
Liver chemistry		X	X		X	X	X	X	X	X	X	X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X	X		X		X	X	X	X		X
c-peptide and 1,5 –Anhydroglucitol (1,5 AG)	Will be performed at central lab if not available at local lab	X	X							X		X		X	
Hemoglobin A1c		X	X							X		X		X	
Fasting lipids		X	X							X		X		X	X
Thyroid monitoring	Thyroid stimulating hormone (TSH), free T3, free T4. If TSH is abnormal W1D1, monitor TSH, free T3 and free T4 going forward	X	X							X		X		X	X
Urinalysis		X	X							X		X		X	X
Pregnancy test, females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X							X		X	X		X
Testosterone, males	Complete and free testosterone at	X	X							X		X	X		X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
	SCR; free testosterone thereafter														
CK, CK-MB	Predose and 12-18 h post dose		X	*as clinically appropriate*											
Safety Cytokines	This is collected as part of the Predose PK sample and is sent to GSK DMPK.	X	*as clinically appropriate following fever*												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X													

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

1. If any parameter (i.e., platelets) shows a downward trend, additional analyses should be performed within 2-3 days to monitor.

Table 9 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1										W1D5		W2D4 + 1 day			
	pre dose	15 min ± 5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	16h ±2h	24h ±2h	33h ±3h	30 min ±5m	3h ±15m	pre dose	30 min ±5m	3h ±15m	8h ±1h
12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sampling	X	0-2h			2-24h											
mRNA whole blood sample	X				X	X	X		X	X						
LPS whole blood sample	X	X	X	X	X	X										

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment (pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr) and acute phase protein assessment at pre-dose and at 2,4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed. .

On serial PK sampling days, subjects enrolled in the serial PK cohort should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days										**W9D1 ±4 days** (if dose has been escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±4h**	**24h ±1h**	**48h ±1h**	**pre dose**	**0.5-2h**	**4 - 8h**	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine PK sampling		0-2h			2-24h									
mRNA whole blood sample	X													X
LPS whole blood sample														

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment at pre-dose and at 2, 4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.
On serial PK sampling days, subjects enrolled in the serial PK cohort should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose.

8.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race, and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

8.2.1. Critical Baseline Assessments

The following are required at baseline:

- imaging (e.g., CT of the Chest/Abdomen/Pelvis or MRI of the Abdomen/Pelvis) at the discretion of the investigator, based on the subject's disease. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required.
- cardiology evaluation including echocardiogram, 12-lead ECG and Holter monitoring

8.2.2. Visit Windows

Screening (baseline to pre-dose): All assessments should be completed within 14 days prior to screening. Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Week 1: Based on subject and clinic schedule, Week 1 Day 3 assessments can be ± 1 day.

Week 2 to Week 4: Based on subject and clinic schedule, assessments can be +3 days.

Week 4 to Week 9: Clinic visits can be scheduled ±3 day.

Monthly visits after Week 9 until Week 52: After the first disease assessment has been completed then the month clinic visits can be scheduled ± 5 days.

Monthly visits after Week 52: clinic visits can be scheduled ± 7 days.

Discontinuation visit: should be 14 to 28 days from last dose of study drugs. If a subject is unable to return to the clinic due to hospitalization, site staffs are encouraged to telephone the subject for assessment of adverse events.

8.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 8.1). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Note that this section details the procedures used to evaluate for safety and toxicity for this study. For management and recording of any suspected Adverse Events, refer to Section 9, Appendix 6 and Appendix 7.

8.3.1. Physical Exams

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses

8.3.2. Performance Status

The performance status will be assessed using the ECOG scale (Appendix 2) as specified in the Time and Events Table (Section 8.1).

8.3.3. Vital Signs

- Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
    - In case of an abnormal first reading, three readings of blood pressure and pulse rate should be taken, the first reading should be rejected and the second and third averaged to give the measurement to be recorded in the CRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

Refer to the Study Reference Manual (SRM) for details regarding measurement of vital signs.

8.3.4. Echocardiogram

For all subjects, trans-thoracic echocardiograms (TTEs) will be performed at screening and at assessment times as outlined in Table 7. TTEs should be evaluated and compared to baseline by the same reader. Copies of all TTE scans performed on subjects who experience an absolute decrease >10% in left ventricular ejection fraction (LVEF) compared to baseline concurrent with LVEF < LLN will be required by GSK for review.

TTE data may be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying TTE scans are provided in the SRM.

8.3.5. Safety Electrocardiograms (ECG)

Safety ECGs will be performed at the time points specified in Table 7 using a standard 12-lead ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Details will be provided in the SRM.

8.3.5.1. Routine ECG Monitoring

Triplicate 12-lead ECGs should be performed at Screening and at all other time points, including on Serial Pharmacokinetic sampling days.

Standard 12-lead ECGs (Safety ECGs) will be performed as part of the real-time assessment of subjects and may not be included in the primary QT analysis. Safety ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

ECG data may be transferred and reviewed by an independent central reviewer. Instructions for submission of ECGs are provided in the SRM.

8.3.5.2. Evaluation of QTc

All ECGs must include QTcF measurements. For the definition of QTcF and management strategies for QTcF ≥ 500 msec, see Section 5.4.2 and Appendix 7.

8.3.6. Telemetry

In addition to Safety ECG assessments, monitoring for potential adverse arrhythmias will be conducted utilizing continuous inpatient telemetry monitoring as outlined in Table 7 for at least 48 hours from the start of the first dose. If clinically indicated, telemetry may be extended past 48 hours. Participating sites will have trained staff capable of monitoring and responding in real time to any potential cardiac adverse event detected by telemetry. In addition, emergency resuscitation equipment including appropriate pharmacological agents will also be immediately accessible.

8.3.7. Holter Monitoring

In addition to the Safety ECGs performed during the study, continuous 12-lead ECGs (obtained via a Holter monitor) will be acquired while subjects are at the site. Dual snap electrodes will be utilized to enable simultaneous collection of Holter and safety ECG data.

Digital Holter ECG data will be obtained from 12-lead continuous Holter monitoring device supplied by the Sponsor. ECG acquisition via the Holter monitoring device will be performed at planned time points indicated in the Time and Events and should be obtained prior to phlebotomy and vital sign time points.

Collection of critical ECG data shortly after meals or during sleep should be avoided since QT prolongation occurs at these times and a change in the QT-RR relationship occurs during sleep. Meals should be administered according to the guidelines provided in Section 7.2 and in the SRM as meal and snack times will need to be adjusted accordingly on dosing and ECG sampling days.

Analysis of intervals and morphology from the continuous digital ECG data will be acquired and stored electronically and manually over-read by an external central validated ECG laboratory. Around each of the designated time points, 3 ECGs will be selected approximately 2 minutes apart. In order to increase consistency of ECG interpretation, a limited number of central ECG over-readers will be used throughout the study. All ECGs for a given subject will be over-read by the same reader from the central validated ECG laboratory. The central reader will be blinded to subject identifiers (e.g., subject number, age, and sex), treatment assignment, and study day when Holter ECGs were collected. The final intervals and morphology analyses entered into the database will be those generated by the central ECG laboratory.

Baseline QT/QTcF values will be determined on Study Day -1 using time matched ECGs obtained from the Holter monitor at approximately the same time points as planned for: Week 1 Day 1 to 2; Week 2 Day 3 to 4, Week 3 Day 5 to 6 and Week 4 Day 7 to Week 5 Day 1. The mean from triplicate ECGs will be evaluated at each time point. For a given time point, the mean QTcF from 3 separate beats should be analyzed on each ECG. Analysis of Lead II will be conducted with V5 as back-up and one of the remaining precordial leads as an alternative when T waves are not well defined in Leads II or V5. QTcF for an individual beat will be calculated from the preceding RR interval since using the average heart rate (RR) intervals from the ECG could result in inaccurate QTcF calculations due to beat to beat variations in the RR intervals.

QT values should not be reported when the rhythm is other than sinus rhythm (sinus rhythm with normal respiratory variation is acceptable), and in intraventricular conduction delays (IVCD, QRS >120 msec). The other ECG information (including the rhythm and presence of IVCD) should be reported. The choice of the 3 consecutive beats to be measured should avoid ectopic beats and the first beat after an ectopic beat. If IVCD occur, these should be reported.

8.3.8. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 11, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All protocol required safety laboratory assessments, as defined in Table 11, are performed at the institution's local laboratory. All non-safety assessments (e.g., pharmacokinetic samples and translational samples) will be assessed by a central laboratory. Please refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Some laboratory assessments (e.g., testosterone) can vary throughout the day. It is recommended but not mandated that laboratory assessments are collected at approximately the same time on each clinic day. If abnormal testosterone levels are observed, repeat measurements should occur at the approximate baseline timing to ensure this is a trend and not a single outlying event.

Table 11 Clinical Laboratory Tests

Serum Chemistry			
Blood urea nitrogen	Magnesium	aspartate aminotransferase	Total and direct bilirubin
Sodium	Potassium		Uric acid
Creatinine	Chloride	alanine aminotransferase	Albumin
Fasting Glucose	Total carbon dioxide	alkaline phosphatase	Total protein
Creatine phosphokinase	Ionized calcium	gamma-glutamyltransferase	Total calcium
Hematology			
Platelet count	*Automated White Blood Cell*		
Red blood cell count	*Differential:*		
White blood cell count (absolute)	Neutrophils (absolute)		
Hemoglobin	Lymphocytes (absolute)		
	Monocytes (absolute)		
	Eosinophils (absolute)		
	Basophils (absolute)		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			

Other Tests
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)
Pancreatic markers (amylase and lipase)
Fasting Lipid panel (triglycerides and total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL])
C-Peptide
Troponin (I or T at local laboratory, Troponin T at central laboratory]
Insulin
Hemoglobin A1C
1,5 –Anhydroglucitol (1,5 AG)
NT-proBNP
Thyroid-stimulating hormone (TSH)
Free Thyroxine 3 (Free T3)
Free Thyroxine 4 (Free T4)
Creatine kinase (CK)
Creatine Kinase-MB (CK-MB)
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose)
Pregnancy test for females (serum at screening, Urine or serum post dose)
Cytokine samples

Subjects should be instructed to fast (no food and only water allowed) for 10 hours prior to any fasting laboratory assessments (e.g., fasting glucose, fasting lipid panel, etc.).

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be recorded on the eCRF as AEs. In addition, these clinically significant abnormal laboratory results should be followed until the abnormality resolves or is determined to be stable. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.3.9. Troponin Measurement

Two samples for troponin will be collected at each time-point as outlined in Table 8. Troponin T will be assessed at a central laboratory as a means of consistent evaluation across all subjects. A second sample will be assessed at a local laboratory for purposes of subject management. Whenever possible, troponin T will be assayed by the local laboratory. However, either troponin I or troponin T may be assessed at a local laboratory. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study.

8.3.10. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 14 days following the last dose of GSK2820151.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

8.4. Pharmacokinetics

PK analyses will be the responsibility of GSK Clinical Pharmacokinetics Modeling & Simulation (CPMS). Plasma GSK2820151 concentration-time data will be analyzed by non-compartmental methods with WinNonlin.

From the plasma concentration-time data, the following pharmacology parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC(0-τ) and AUC(0-∞) Week1 Day1 only) and apparent terminal phase half-life (t½). Trough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined from the ratio of AUC(0-τ) in Week 3 Day 4 / AUC(0-τ) in Week 1 Day 1. The ratio of AUC(0-τ) on Week 3 Day 4/ Week 1 Day 1 AUC(0-∞) will be calculated to assess time invariance. GSK2820151 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

Plasma concentration-time data will be listed by dose and summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) PK parameters values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters [if applicable]) by dose cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are evaluated, dose proportionality of AUC and Cmax for GSK2820151 will be assessed using the power model (details will be provided in the Reporting and Analysis Plan [RAP]).

Plasma concentration-time data will be further analyzed using appropriate model(s) to determine population PK parameters (absorption rate (Ka), apparent clearance (CL/F) and volume of distribution (V/F)) and summary exposure measures (Cmax, AUC and Average observed concentration (Cav) = AUC/τ) and identify important covariates (e.g., age, weight, or disease related covariates).

8.4.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of GSK2820151 will be collected at the time points indicated in the Time and Events Schedule (Table 9 and Table 10).

Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded along with the date and time of the prior dose administration. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. This will not require a protocol amendment.

Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM.

8.4.2. Urine Sample Collection for Pharmacokinetics

Urine samples for quantitative analysis of GSK2820151 will be collected over 24 hours in two samples (sample collected 0-2 hr and a second sample collected 2-24 hr) immediately following dosing on Week 1 Day 1 and Week 3 Day 4

The actual date and time of each urine sample collection will be recorded.

Details of urine sample collection, processing, storage, and shipping procedures are provided in the SRM.

8.4.3. Pharmacokinetic Sample Analysis

Plasma sample analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics (DMPK), Platform Technology and Science (PTS), GlaxoSmithKline. Concentrations of GSK2820151 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be stored in the Good Laboratory Practices (GLP) Archives, GlaxoSmithKline.

Once the plasma samples have been analyzed for GSK2820151, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

Urine sample analysis may be performed under the management of Bioanalytical Science and Toxicokinetics, DMPK, PTS, GlaxoSmithKline. Concentrations of GSK2820151 may be determined in urine samples using an investigative analytical methodology. Urine raw data will be stored in the GLP Archives, GlaxoSmithKline.

The urine samples may be analyzed for compound-related metabolites and the results will be reported under a separate DMPK protocol.

8.5. Pharmacokinetic/Pharmacodynamic Analysis

Observed or predicted concentrations and/or exposures will be combined with safety, efficacy, and/or PD measures of interest to examine potential exposure response relationships.

The relationship between QTcF and concentration expressed as Cmax, Cav, and instantaneous time-matched concentration will be plotted graphically. A linear mixed effects analysis of the slope of the QTcF-concentration responses adjusting for baseline will be evaluated as a means of estimating QTcF effect in lieu of a thorough QT study.

Other quantitative safety parameters and biomarkers of interest including changes in troponin levels will be plotted graphically against summary exposure measures (e.g., Cmax, $C\tau$, and Cav). Where evidence of a signal is seen, linear and non-linear mixed

effect models will be fitted to the data to estimate PK/PD parameters of interest; slope, baseline (E0), exposure producing 50% of the maximum effect (EC_{50}), and maximum effect (Emax).

Overall efficacy data and overall tumor burden may be described using ordered categorical model and continuous models with summary exposure parameters (e.g., Cmax, Cτ, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the RAP.

8.6. Efficacy

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per RECIST 1.1.

- Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009] as outlined below and in Appendix 8.
- Disease assessment modalities may include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions).
- The baseline disease assessment will be completed within 2 weeks prior to the first dose of GSK2820151, then every 8 weeks thereafter, and at the final study visit. See the Time and Events Table (Section 8.1) for the schedule of assessments of anti-cancer activity.
- For subjects with CRPC without measurable disease by RECIST criteria, serial prostate specific antigen (PSA) measurements will be drawn at the disease assessment time points defined in the Time and Events Table (Section 8.1). Response will be defined by the number of subjects who achieve a 50% decrement in their baseline PSA (PSA50).
- Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.
- Subjects whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator.
- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

8.7. Translational Research

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be addressed in the RAP.

8.7.1. Biologic Effects of GSK2820151

Exploratory analysis may be performed to examine potential relationships between drug exposure and markers of BET target inhibition (e.g., cytokines, acute phase proteins, relevant transcripts, and/or proteins) or between anticancer activity and potential markers of sensitivity (e.g., genetic alterations).

8.7.2. RNA Expression Research

Related BET inhibitors have been shown to modulate the expression of a number of different genes in unstimulated whole blood between 1 h and 6 h. The mRNA levels of 31 such genes form a 'signature' panel which will also be used as a biomarker of engagement of pharmacology and will be measured using mRNA isolated from whole blood. The modulation of a number of these genes will also be measured as changes in systemic proteins as well as in the analysis of the ex vivo assay blood samples (e.g., CCL2 and IL-8) thus relating mRNA and protein expression with drug concentration. Other translational research studies, such as transcriptomics profiling, will also be performed using whole blood mRNA from selected patients.

8.7.3. Effects of GSK2820151 on Systemic Markers of Inflammation

GSK2820151 has been shown to inhibit LPS-induced IL-6 across different human cell populations and species. The action of the compound is through inhibition of the assembly of transcriptional complexes required to express the protein. Pre-clinical studies demonstrate that blood concentration of drug correlates to the degree of inhibition of LPS induced IL-6 in ex vivo whole blood samples. Therefore, this biomarker will be used as an indication of pharmacology and will be aligned with PK sampling. Since inhibition of BET family proteins is known to inhibit a range of pro-inflammatory mediators and acute phase proteins, a number of additional proteins (46) will also be measured from these ex vivo samples.

The set of analytes identical to that used in the whole blood ex vivo assay (including for example, CCL2, MIP1-α, IL-8) will also be measured in plasma samples taken during PK sampling and at the time of any Grade 2 fever or symptoms indicative of a potential cytokine storm. This will assess systemic inflammatory response in the subject using biomarkers such as pro-inflammatory cytokines and acute phase proteins and correlate the systemic response to drug with that in stimulated and unstimulated blood. These biomarkers are expected to change over days rather than hours, based on the plasma half lives and pre-clinical data, such that sampling will also be performed after repeat dosing.

8.8. Pharmacogenetic Analysis

An important objective of the clinical study is pharmacogenetic (PGx) research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in host DNA from blood will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics, and efficacy) to treatment with GSK2820151.

Information regarding pharmacogenetic research is included in Appendix 4. In approving the clinical protocol, the independent ethics committee/institutional review board (IEC/IRB) (and, where required, the applicable regulatory agency) also approve the PGx assessments unless otherwise indicated. Where permitted by regulatory authorities, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

Information regarding genetic research is included in Appendix 4.

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DATA COLLECTION, REPORTING, AND FOLLOW-UP

9.1. Definition of AE/SAE

The definitions of an AE or SAE can be found in Appendix 6. The severity of adverse events will be graded utilizing the NCI-CTCAE v4. Additional details regarding management of specific AEs or SAEs are described in Appendix 7.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

9.1.1. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 6 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.1.2. Other Sentinel Events

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

9.1.3. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

NOTE:If either of the following conditions apply, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

9.2. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 9.2.2), at the timepoints specified in the Time and Events Table (Section 8.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5

9.2.1. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

9.2.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

9.2.3. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

10. DATA MANAGEMENT

For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

11. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

11.1. Hypotheses

The primary endpoints of this study are safety and tolerability; the MTD and RP2D will also be determined. No formal statistical hypotheses will be tested. The primary focus will be on determining the recommended dose for further exploration, the safety profile, and the PK of GSK2820151 in subjects with advanced cancer. Analyses will be descriptive and exploratory.

11.2. Continual Reassessment Method

11.2.1. Description of Continual Reassessment Method

After all subjects in each cohort have completed the DLT observation period, a dosing recommendation for the next cohort will be made following an N-CRM analysis. All available data, including safety and PK data from current and prior cohorts will be reviewed at the dose escalation meeting. Although the N-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor in consultation with the study team and Investigators, and taking into account PK and PD data, will determine dose escalation as deemed appropriate.

The N-CRM design makes use of a Bayesian logistic regression model relating dose and toxicity and is expected to locate the MTD efficiently while minimizing the number of subjects exposed to pharmacologically inactive or unsafe dose levels.

The MTD will be defined as that dose that has the highest posterior probability of having a DLT rate within the Target Toxicity range and for which the posterior probability that

the DLT rate lies within the Excessive Toxicity or the Unacceptable Toxicity range is less than 25%.

The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- A dose falls in the **Under-dosing** range if the probability of a DLT at the dose is 0% - 16%
- A dose falls in the **Target** Toxicity range if the probability of a DLT at the dose is 16% - 33%
- A dose falls in the **Excessive** Toxicity range if the probability of a DLT at the dose is 33% - 60%
- A dose falls in the **Unacceptable** Toxicity range if the probability of a DLT at the dose is 60% - 100%

An updated posterior estimate of the dose-toxicity curve will also be provided at the time of the dose-escalation meeting.

11.2.1.1. Implementation of N-CRM

The N-CRM model implementation will be performed using the Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 2.3 or higher) software from Tessella.

11.2.1.2. Bayesian Prior

The N-CRM methodology requires that a Bayesian prior distribution for the dose-toxicity curve be pre-specified. The Bayesian prior used for this design was determined using the quantile method. For each dose, the most likely (median) presumed probability of DLT was specified, along with a 95% credible interval – an interval within which the team is 95% a priori certain the probability of a DLT lies. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK2820151 in humans and to allow the accumulating data to have more influence on dose recommendations than the prior. Further details regarding the specific N-CRM model will be provided in the Reporting and Analysis Plan (RAP) and will be determined before the first dose-escalation meeting after consideration of all information gathered before then.

11.3. Sample Size Considerations

11.3.1. Sample Size Assumptions

The total number of subjects to be enrolled into this study will depend on the number of subjects needed to characterize individual dose cohorts for the determination of the maximum tolerated dose of GSK2820151; the final sample size is not driven by statistical considerations. However, it is anticipated that approximately 30 to 50 subjects will be enrolled with a maximum of 80 subjects.

11.3.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

11.4. Data Analysis Considerations

Data will be listed and summarized according to GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

11.4.1. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2820151. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **PK Population** will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

Additional analysis populations may be defined in the RAP.

11.4.2. Interim Analysis

Interim analyses will be performed to determine if a dose-escalation is appropriate. The primary driver for the dose-escalation decisions will be safety and tolerability of each dose cohort.

11.5. Key Elements of Analysis Plan

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

All data will be summarized and listed.

11.5.1. Primary Analyses

As the primary endpoints of this study are safety and tolerability, the primary analyses will be descriptive in nature. Safety endpoints are described in Section 5.4.

The All Treated Population will consist of all subjects receiving at least one dose of study drug and will be used for the analysis of safety and efficacy data. Complete details of the analyses will be provided in the RAP.

11.5.2. Secondary Analyses

11.5.2.1. Pharmacokinetic Analyses

11.5.2.1.1. Pharmacokinetic Parameters

PK analyses will be the responsibility of CPMS, GSK. Plasma GSK2820151 concentration-time data from dose escalation will be analyzed by non-compartmental methods with WinNonlin.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC(0-t) and AUC(0-∞) Week1 Day1 only) and apparent terminal phase half-life (t½). Trough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined. The ratio of AUC(0-τ) on Week 3 Day 4 AUC(0-τ) / Week 1 Day 1 AUC(0-∞) will be calculated to assess time invariance. GSK2820151 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

11.5.2.1.2. Statistical analysis of pharmacokinetic parameters

Statistical analyses of the PK parameters data will be conducted by Clinical Statistics, GSK. Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) pharmacokinetic parameter values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters [if applicable]) by dose cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data),dose proportionality of AUC and Cmax for GSK2820151 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is

sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

11.5.2.2. Efficacy Analysis

For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the initiation of therapy. Progressive disease (PD) will also be defined per RECIST 1.1 criteria. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. PFS will be summarized using Kaplan-Meier methods.

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per RECIST 1.1 criteria. Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. Exact methods for calculated confidence intervals will be given in the RAP.

The number and types of responses, as outlined in RECIST 1.1, will be listed and summarized, as appropriate.

11.5.2.3. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, electrocardiogram [ECGs]) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the RAP.

11.5.2.4. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy

11.5.2.5. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE v4.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE v 4, will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Dose-limiting toxicities (DLTs) will be listed for each subject and summarized by dose cohort.

AEs of special interest will be outlined in the RAP.

The incidence of deaths and the primary cause of death will be summarized.

11.5.2.6. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Further details will be provided in the RAP.

11.5.3. Other Analyses

Exploratory analyses may be performed to examine potential relationships between anticancer activity and changes in markers of BET target inhibition or tumor biology (e.g., cytokines, acute phase proteins, relevant transcripts, and/or proteins) or between anticancer activity and potential markers of sensitivity.

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details on the translational research analyses will be addressed in the RAP.

12. STUDY GOVERNANCE CONSIDERATIONS

12.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

12.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

12.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

12.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all

relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

12.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

12.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

12.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

13. REFERENCES

Asangani IA, Dommeti VL, Wang X, Malik R, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature. 2014; 510(7504): 278-82.

Bauer DE, Mitchell CM, Strait KM, Lathan CS, et al. Clinicopathologic Features and Long-term Outcomes of NUT Midline Carcinoma. Clin CanRes. 2012; 18:5773-9.

Chaidos A, Caputo V, Gouvedenou K, Liu B, Liu B, et.al. Potent antimyeloma activity of the novel bromodomain inhibitors I-BET151 and I-BET762. Blood 2014; 123(5): 697-705.

Delmore JE, Issa GC, Lemieux ME, Ral PB, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011; 146: 904-917.

Dey A, Chitsaz F, Abbasi A, Misteli T, Ozato K. The double bromodomain protein Brd4 binds to acetylated chromatin during interphase and mitosis. Proc Natl Acad Sci U S A. 2003;100(15): 8758-63.

Dey A, Nishiyama A, Karpova T, McNally J, Ozato K. Brd4 marks select genes on mitotic chromatin and directs postmitotic transcription. Mol Biol Cell. 2009; 20(23): 4899-909.

Dhalluin C, Carlson JE, Zeng L, He C, et. al. Structure and ligand of a histone acetyltransferase bromodomain. Nature 1999; 399: 491–496.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, et al. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). Eur J Cancer. 2009; 45: 228-247.

Fiskus W, Sharma S, Qi J, Shah B, et al. BET Protein Antagonist JQ1 Is Synergistically Lethal with FLT3 Tyrosine Kinase Inhibitor (TKI) and Overcomes Resistance to FLT3-TKI in AML Cells Expressing FLT-ITD. Mol Cancer Ther. 2014; 13(10); 2315–27.

French C, Ramirez C, Kolmakova J, Hickman TT, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene, 2008; 27: 2237-42.

GlaxoSmithKline Document Number 2014N208278_00; GSK2820151 Investigator's Brochure. Version 1.

Hargreaves DC, Horng T, Medzhitov R. Control of inducible gene expression by signal-dependent transcriptional elongation. Cell. 2009; 138(1): 129-45.

Itzen F, Greifenberg AK, Bösken CA, Geyer M. Brd4 activates P-TEFb for RNA polymerase II CTD phosphorylation. Nucleic Acids Res. 2014; 42(12): 7577-90.

James LP. 2009. Pharmacokinetics of Acetaminophen - Protein Adducts ... Liver Failure. Drug Metab Disp, 37: 1779-1784.

Jang MK, Mochizuki K, Zhou M, Jeong HS, Brady JN, Ozato K. The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription. Mol Cell. 2005; 19(4): 523-34.

Mertz J, Conery AR, Bryant BM, Sandy P, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Nat Acad Sci. 2011; 108: 16669-74.

NCI-CTCAE (NCI Common Terminology Criteria for Adverse Events), Version 4.03, DCTD, NCI, NIH, DHHS, June 14, 2010.

Neuenschwander B, Branson M, and Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008 27: 2420–39.

Nicodeme E, Jeffrey K, Schaefer U, Beinke S, et al. Suppression of inflammation by a synthetic histone mimic. Nature 2010; 478: 1119-1123.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group, 1982.

Patel MC, Debrosse M, Smith M, Dey A, et.al. BRD4 coordinates recruitment of pause release factor P-TEFb and the pausing complex NELF/DSIF to regulate transcription elongation of interferon-stimulated genes. Mol Cell Biol. 2013; 33(12): 2497-507.

Trabucco SE, Gerstein RM, Evens AM, Bradner JE, et al. Inhibition of bromodomain proteins for the treatment of human diffuse large B-cell lymphoma. Clin Cancer Res. 2014 Jul 9. pii: clincanres.3346.2013. [Epub ahead of print]

Wyce A, Ganji G, Smitheman KN, Chung CW, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PLoS One 2013;8:e72967.

Yan J, Diaz J, Jiao J, Wang R, You J. Perturbation of BRD4 function by BRD4-NUT abrogates cellular differentiation in NUT midline carcinoma. J Biol Chem. 2011; 286:27663-27675.

14. APPENDICES

14.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

°C	Degrees Celsius
1,5 AG	1,5 –Anhydroglucitol
A1c	Glycosylated hemoglobin
ACLS	Advanced Cardiac Life Support
AE(s)	Adverse eEvent(s)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-∞)	Area under the curve from zero to infinity
AUC(0-24)	Area under the curve from zero to 24 hours
AUC(0-τ)	Area under the plasma concentration-time curve
BAL	Bronchoalveolar lavage
BCRP	Breast Cancer Resistance Protein
BET	Bromodomain & extra-terminal
BID	Twice daily
BPM	Beats per minute
BRD	Bromodomain
CBC	Complete blood count
CCL2	Chemokine (C-C motif) ligand 2
CK	Creatine kinase
CK-MB	Creatine kinase, MB isoenzyme
C_{min}	Minimum observed plasma concentration
C_{max}	Maximum observed plasma concentration
COPD	Chronic obstructive pulmonary disease
CPMS	Clinical Pharmacokinetics Modeling & Simulation
CR	Complete response
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
C_τ	Trough concentration
CV	Cardiovascular
CV	Coefficient of variance
DHEA	Dehydroepiandrosterone
dl	Deciliter(s)
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EC50	Exposure producing 50% of E_{max}
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	Electronic case report form
EIAC	Enzyme-inducing anticonvulsant
E_{max}	Maximum effect
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FSH	Follicle Stimulating Hormone
FTIH	First time in human
g	Gram(s)
GCP	Good clinical practice
GI	Gastrointestinal
gIC50	Growth inhibitory concentration 50
GLP	Good laboratory practices
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
hERG	Human *ether-à-go-go*-related gene
HIV	Human immunodeficiency virus
HNSCT	Highest non-severely toxic dose
hr	Hour(s)
HRT	Hormone replacement therapy
IC_{50}	half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent ethics committee/institutional review board
IL-6	Interleukin 6
IL-8	Interleukin 8
INR	International normalized ratio
IRB	Institutional review board
IUD/IUS	Intrauterine device/intrauterine system
IV	Intravenous
IVCD	Intraventricular conductance delay
kg	Kilogram(s)
l	Liter(s)
LDL	Low-density lipoprotein
LHRH	Luteinizing hormone releasing hormone
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LPS	Lipopolysaccharide
LVEF	Left ventricular ejection fraction
m^2	Meters squared
MABEL	Minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MI	Myocardial infarction
min	Minute(s)
MIP1-α	Macrophage inflammatory protein 1 alpha

mIU	Milli International Units
ml	Milliliter(s)
μM	Micromolar
mm^3	Cubic millimeters
MM	Multiple myeloma
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSDS	Material safety data sheet
msec	Millisecond(s)
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
MYC	V-myc avian myelocytomatosis viral oncogene homolog
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
N-CRM	Neuenschwander - Continuous Reassessment Method
ng	Nanogram(s)
NMC	NUT midline carcinoma
NOAEL	No observed adverse effect level
NOD/SCID	Non-obese diabetic/severe combined immunodeficiency
NT-proBNP	N-terminal pro–B-Type natriuretic peptide
NUT	Nuclear protein in testes
NYHA	New York Heart Association
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression-free survival
pg	Picogram(s)
PgP	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetic
pmol	Picomole(s)
PR	Partial response
PSA	Prostate specific antigen
PSA50	50% decrement in baseline PSA
PT	Prothrombin time
p-TEFB	Positive transcription elongation factor complex
PTS	Platform Technology & Science
PTT	Partial thromboplastin time
QTc	Corrected QT interval
QTcF	Corrected QT (Fridericia's formula)
RAP	Reporting and Analysis Plan
RECIST	Response criteria in solid tumors
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose

SAE(s)	Serious adverse event(s)
SD	Standard deviation
SD	Stable disease
SPM	Study Procedures Manual
SRM	Study Reference Manual
SRT	Safety review team
STD10	Severely toxic dose in 10% of the animals
$t_{½}$	Half-life
t_{max}	Time to C_{max}
TSH	Thyroid Stimulating Hormone
TSS	Transcription start site
TTE	Transthoracic echocardiogram
ULN	Upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
WinNonlin

14.2. Appendix 2: ECOG Performance Status

The performance status assessment is based on the ECOG scale [Oken, 1982]

0 = Fully active, able to carry on all pre-disease performance without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 = Dead.

14.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject <u>with</u> entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥ 5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 4) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • Blood sample for pharmacokinetic (PK) analysis, obtained 2 days after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

14.4. Appendix 4: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

Background Information on Drug Restart/Rechallenge

1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [**Andrade**,** 2009**]**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 9.

2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an

HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 9.

References:

- Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
- Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.
- Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

14.5. Appendix 5: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and response to medicine, including GSK2820151 or any concomitant medicines.

US Food and Drug Administration states that an *in vitro* companion diagnostic device (IVD) could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from a particular therapeutic product;
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product;
- Monitor response to treatment for the purpose of adjusting treatment (e.g. schedule, dose, discontinuation) to achieve improved safety or effectiveness

Global regulatory requirements for IVD companion diagnostic tests are evolving. If a DNA-based IVD companion diagnostic device might be needed to identify patients who are appropriate for the GSK medicinal product(s) under investigation in this protocol, then GSK should collect and retain DNA samples from subjects who carry the genetic variant of interest as well as DNA samples from subjects who do not carry the genetic variants of interest to validate the performance of the companion diagnostic. Any IVD companion diagnostic research objectives should be described in subject informed consent forms.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in the RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

14.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

14.6.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

14.6.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
e. Results in death
f. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
g. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

h. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

i. Is a congenital anomaly/birth defect

j. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

k. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Refer to Appendix 2 for the required liver chemistry follow-up instructions

14.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

14.6.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

14.6.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

14.6.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and e-mail it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

14.7. Appendix 7: Guidelines for Management of Toxicity

The following dose modification criteria should provide guidance for, but not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that drug. Dose modifications should be made after discussion with the GSK medical monitor.

14.7.1. Dose Adjustments for Toxicity

Table 12 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	• Continue current dose of GSK2820151 • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4mol/L (2) Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	• Discontinue GSK2820151 and notify the GSK Medical Monitor. (1) Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L (2) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (3) Discontinue any concomitant medications with potential for QTcF prolongation. (4) Consider telemetry monitoring if clinically indicated. • This subject may consider restarting study treatment at a previous dose level if the following criteria for QTcF rechallenge are met: • QTcF Rechallenge Procedures: Do not rechallenge with study treatment unless under the following conditions: (1) QTcF event reduced to <450 msec, (2) potassium and magnesium levels are within institutional normal range, (3) a favorable risk/benefit profile (in the medical judgement of the Investigator and the GSK Medical Monitor),

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		(4) approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. • If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be monitored weekly for two weeks, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN	• Evaluate immediately for symptoms and obtain ECG. Repeat troponin within 24-48 hours or as soon as possible. • If the repeat value is within the normal range, the subject may continue GSK2820151 with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. • If the repeat value remains > ULN AND the subject is asymptomatic, hold GSK2820151, refer to a cardiologist, and contact the GSK Medical Monitor • If the subject is symptomatic OR the troponin level approaches the threshold for mycocardial infarction (MI) according to local lab parameters, hold GSK2820151 and refer the subject immediately to a cardiologist or emergency medical facility for appropriate medical care. • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines

LVEF	Ejection fraction below the institution's lower limit of normal (LLN)
	
	<u>AND</u>
	
	An asymptomatic, absolute decrease of >10% in LVEF compared to baseline
		• Temporarily discontinue GSK2820151 and repeat evaluation of LVEF within 2 weeks
		  • If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on GSK2820151 at a reduced dose.
		  ○ Monitoring should be performed at 2 and 4 weeks after restarting GSK2820151 and then per protocol specifications.
		  • If LVEF does not recover within 4 weeks, permanently discontinue GSK2820151. Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines

	Grade 3 or 4	• Permanently discontinue GSK2820151.
		  • Evaluation by a cardiologist required.
		  • Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution.

Liver		Refer to procedures outlined in Appendix 3: Liver Safety Required Actions and Follow up Assessments
Hypo- and Hyperglycemia Note: for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE version 4 Grade 1-5	(Mild) Fasting blood glucose >150 mg/dL	• Monitor fasting and preprandial glucose.

	(Moderate to Severe) Fasting blood glucose <70 mg/dL OR any blood glucose >250 mg/dL	• Hold GSK2820151 and instruct subject to notify investigator immediately.
		  • If a blood glucose >250 mg/dL is observed, the subject should be evaluated for ketoacidosis as clinically indicated.
		  ○ This may necessitate inpatient management.
		  ○ The action of insulin or other antihyperglycemic agents should be restored as study medication is cleared. If an antihyperglycemic agent is administered, then the subject should be observed closely for rebound hypoglycemia as the study medication is cleared.
		  ○ Intravenous insulin treatment is recommended.
		• May consider restarting GSK2820151 at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.

Diarrhea	Grade 1	• Initiate supportive care including loperamide.
	Grade 2	• Initiate supportive care including loperamide. • Consider temporary discontinuation of GSK2820151 and discuss with GSK Medical Monitor.
	Grade 3	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Hold GSK2820151 and discuss with GSK Medical Monitor. • If diarrhea recovers to less than Grade 2, discuss with medical monitor; consider resuming treatment at the same or lower dose based on clinical judgement.
	Grade 4	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Discontinue GSK2820151 permanently

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Mucositis	Grade 1 or 2	• Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
	Grade 3 or 4	• Above, plus systemic opiate administration as needed. • Consider IV hydration and hospital admission as appropriate. • May restart GSK2820151 at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines

Pneumonitis	Grade 1	• Continue GSK2820151 at current dose.
		• Consider evaluation by pulmonologist.
		  • Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to baseline.
		  • Obtain high-resolution computed tomography (CT) scan of the chest if possible.

	Grade 2	• Hold GSK2820151 until recovery to < Grade 1, then reduce dose by at least 25%.
		• Consider evaluation by pulmonologist.
		  • Consider pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to baseline.
		  • Obtain high-resolution chest CT if possible.
		  • Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL).
		  • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated.
		• Discontinue GSK2820151 if no recovery to <Grade 1 within 4 weeks. May consider escalation to pre-event dose after discussion with GSK Medical Monitor

	Grade 3 or 4	• Hold GSK2820151 and refer for evaluation by pulmonologist
		  • Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to baseline.
		  • Obtain high-resolution chest CT if possible.
		  • Bronchoscopy with biopsy and/or BAL is recommended.
		  • Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.
		• Rechallenge Guidelines
		  • Grade 3: Hold GSK2820151 until recovery to < Grade 1. Discontinue GSK2820151 if no recovery to < Grade 1 within 4 weeks. May consider restarting

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		GSK2820151 at a reduced dose after discussion with GSK Medical Monitor if there is clinical benefit. • Grade 4: Rechallenge with GSK2820151 is not permitted
Fever	Grade 1	• Continue current dose of GSK2820151 and monitor for change in severity.
	Grade 2	• Temporarily discontinue GSK2820151 and monitor for change in severity. • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. Assess vital signs. • Collect cytokine blood samples as outlined in the SRM. Collect blood culture and investigate viral infections as applicable • Consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.
	Grade 3 or 4	• Temporarily discontinue study medication and monitor for change in severity. • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. • Collect cytokine blood samples as outlined in the SRM. Collect blood culture and investigate viral infections as applicable. • Consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor
Thrombocytopenia	Grade 1 or 2 (Count ≥ 50,000)	• Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (Count 25,000 – 50,000)	• After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider reduced daily dosing or dosing on alternate days). Monitor CBC at least twice a week, more frequently if necessary
	Grade 4 (Count ≤ 25,000)	• Interrupt study medication and monitor CBC every 2-3 days. • If platelet counts recover to Grade 2, discuss with medical monitor resuming treatment at the same or adjusted dose based on sound clinical judgement. • Platelet transfusion is allowed based on

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		institutional guidelines. In case of platelet transfusion, hold drug for at least 7 days from day of transfusion, and if platelet counts recover to Grade 2 consider initiating treatment at a lower dose using sound clinical judgement and after consulting with the GSK medical monitor. • Discontinue treatment if drug has to be held for >14 days or greater than 2 dose reductions are required.
All Other Toxicity*	1	• Continue dosing with no change
	2	• Continue dosing with no change OR • Hold GSK2820151 for up to 1 week for toxicity to be < Grade 2, then continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	3	• 1st episode: Hold dose for one week intervals until ≤ drug-related Grade 2, then restart with no change. • 2nd episode: Utilize an alternative, less frequent schedule or reduce by one dose level. • If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.
	4	• Discontinue GSK2820151 • In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the subject is receiving benefit then the episode may be managed as per Grade 3 toxicity.

*Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for certain AEs as defined in Section 4.2.5.

14.8. Appendix 8: Guidelines for Assessment of Disease, Disease Progression, and Response Criteria – adapted from RECIST 1.1 [Eisenhauer, 2009]

14.8.1. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules) [Eisenhauer, 2009].

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

14.8.2. Guidelines for Evaluation of Disease

14.8.2.1. Measurable and Non-measurable Definitions

14.8.2.1.1. Measurable lesion

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

14.8.2.1.2. Non-measurable lesion

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

14.8.3. Baseline Documentation of Target and Non-Target Lesions

- All baseline lesion assessments must be performed within [28] days of randomization.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

14.8.4. Response Criteria

14.8.4.1. Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

14.8.4.2. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

14.8.4.3. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

14.8.4.4. Evaluation of overall response

Table 13 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 13 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Table 14 presents the overall response at an individual time point for all possible combinations of tumor responses in non-target lesions with or without the appearance of new lesions for subjects with non-measurable only disease at baseline.

Table 14 Evaluation of Overall Response for Subjects with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=Not Evaluable		

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.8.4.5. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 49 days (based on the expected 56 ± 7 day window)
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

14.8.4.6. Confirmation Criteria

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

Reference

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). Europena Journal of Cancer. 2009; 45: 228-247.

14.9. Appendix 9: Cockcroft and Gault Method for Calculated Creatinine Clearance

Calculated creatinine clearance (mL/min) =	(140 – age [yrs]) × weight (kg)
	72 × serum creatinine (mg/100mL)
Female patients: multiply by 0.85	

Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976; 16: 31-41.

14.10. Appendix 10: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- **Any female subject who becomes pregnant while participating:**
    - will discontinue study medication
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.