TITLE PAGE

Protocol Title: A single-centre, randomized, double-blind, dose-ascending, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of oral TID doses (one day) of GSK2982772 in Japanese healthy male subjects

Protocol Number: 205037

Short Title: Phase I study of GSK2982772 in Japanese healthy male subjects

Compound Number: GSK2982772

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Regulatory Agency Identifying Number(s): Not applicable

Approval Date: 7-JUN-2018

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1. SYNOPSIS

Protocol Title: A single-centre, randomized, double-blind, dose-ascending, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of oral TID doses (one day) of GSK2982772 in Japanese healthy male subjects

Short Title: Phase I study of GSK2982772 in Japanese healthy male subjects

Rationale:

This study is the first administration of GSK2982772 to Japanese. The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of oral doses of TID doses for one day with GSK2982772 in Japanese healthy male subjects. GSK2982772 or placebo will be administered at 0 hr (the first dosing), 7 hr (the second dosing) and 14 hr (the third dosing) on Day 1 in each period. The intention of this study is to provide sufficient confidence in the safety of the molecule to inform progression to further repeat dose studies in patients. The dose range proposed in this study is based on a low starting dose escalating to the highest dose that is intended for the Phase 2b dose range study.

Objectives and Endpoints:

Objectives	Endpoints
To assess the safety and tolerability of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Adverse events (AEs) Change in laboratory values (clinical chemistry, haematology and urinalysis), 12-lead ECG and cardiac telemetry, vital signs (blood pressure, pulse rate, and body temperature) Physical examinations, including neurological examinations
To characterise the PK profile of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr (AUC(0-24)) and AUC over each dose interval (i.e. AUC(0-7), AUC(7-14) and AUC(14-24)), maximum observed plasma drug concentration (Cmax) following each dose, time to maximum observed plasma drug concentration (Tmax) following each dose, terminal half-life (t1/2) following the third dose, observed trough plasma drug concentrations (C0, C7, C14 and C24), where data allow

Overall Design:

This study will be a double-blind with respect to subjects, investigators and site staff (with the exception of the unblinded site pharmacist), TID oral doses for one day,

ascending dose, randomized, placebo-controlled, 4-way crossover study, shown as the table below;

Group	N	Period 1	Period 2	Period 3	Period 4
A	3	Placebo, TID	60 mg, TID	120 mg, TID	240 mg, TID
B	3	60 mg, TID	Placebo, TID	120 mg, TID	240 mg, TID
C	3	60 mg, TID	120 mg, TID	Placebo, TID	240 mg, TID
D	3	60 mg, TID	120 mg, TID	240 mg, TID	Placebo, TID

Number of Participants:

Sufficient Japanese healthy male subjects will be enrolled such that up to approximately 12 subjects complete dosing and critical assessments.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence and start from the period to be replaced at the discretion of the GSK and in consultation with the principal investigator.

Sentinel Dosing:

The doses will be staggered such that for each dose, on Day 1 of Period 1, 2 and 3, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety (AEs, clinical labs, vital signs, 12-Lead ECGs and Cardiac telemetry) in the judgment of the principal investigator and GSK Medical Monitor through at least 24 hrs after their third dose on Day 1, the remaining subjects may be randomized to dosing in that period.

Treatment Groups and Duration:

Screening	Within 30 days prior to the first dose on Day1.
Treatment Period	The study will be comprised of four study periods each at least 7 days in duration with subjects in-house for 4 nights (through 72 hrs after the first dose). During each treatment period, subjects will be admitted to the unit the day before dosing and will be discharged after completion of the 72 hrs post-dose assessments. Each subject will receive oral TID doses of GSK2982772 in each treatment period. For TID dosing, GSK2982772 or placebo will be administered at 0 hr (the first dosing), 7 hr (the second dosing) and 14 hr (the third dosing) on Day 1 in each period. On Day 1, subjects will fast 8hr overnight prior to first dose. A breakfast will be served approximately 2hr after first dose. Lunch and dinner will be served between 2 to 3hr prior to second and third doses, respectively.
Washout Period	Will be at least 7 days between treatment period doses for an individual

	subject.
Follow-up	At least 7 days, and no greater than 14 days after last study treatment administration. If warranted, additional follow-up visits may be scheduled.

2. SCHEDULE OF ACTIVITIES (SoA)

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 Schedule of Activities (SoA) tables, are essential and required for study conduct.

The Study Reference Manual (SRM) will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA tables.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

Time and Events Table for Screening and Follow-up Assessments

Procedure	**Screening[1]**	**Follow-up Visit[2]**	***Notes***
Outpatient Visit	X	X	
Informed Consent	X		
Medical/medication/drug /alcohol history	X		
Demographics	X		
Physical Examination	X	X	*Additional examinations may be performed, by the Investigators, as deemed necessary.*
Drug screen	X		*Additional tests may be performed by the Investigators, as deemed necessary. Tests will be conducted within site specified standards.*
Syphilis, Human immunodeficiency virus (HIV), Human T-cell leulemia virus type 1 (HTLV-1), Hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Tuberculosis (TB) Test	X		Conducted at the standard practice of the site.
X-ray Test	X		Anterior & lateral chest X-ray will be taken.
Hema/Chem/Urinalysis tests	X	X	
Height and weight	X		
12-lead ECG and vital signs	X	X	*Vital signs to include pulse rate (PR), blood pressure (BPs) and temperature.*
AE Review	X	X	*All Serious Adverse Effects (SAEs) will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified. All AEs will be collected from the start of treatment until the follow-up visit at the time points specified.*
Concomitant Medication Review	X	X	

1: Within 30 days prior to the first dosing

2: Follow-up Visit to occur at least 7 days, and no greater than 14 days after last study treatment administration. If a participant withdrew from the study after received GSK2982772 or placebo dose, the safety assessments listed at follow-up visit will be required.

Detailed Time and Events Table for Days 1-4 (common Period1-4)

Procedure [1]	Day -1	Day 1																							
		Pre-dose	0	20 min	40 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	7 hr	7 hr 20 min	7 hr 40 min	8 hr	8.5 hr	9 hr	10 hr	11 hr	12 hr	14 hr	14 hr 20 min	14 hr 40 min	15 hr	15.5 hr
Admission	X																								
Physical Examination	X	X						X				X[6]									X[6]				
Hema/Chem/ Urinalysis tests	X																								
Vital signs [2]		X						X				X[6]									X[6]				
12-lead ECG		X						X				X[6]									X[6]				
Cardiac telemetry [3]			<==========																						
PK blood sampling		X		X	X	X	X	X	X		X	X[7]	X	X	X	X	X	X		X	X[7]	X	X	X	X
Neurological Examination	X							X									X				X[8]				
Study Treatment			X									X									X				
Pharmacogenetic Sampling (PGx) [4]			<==========																						
Meals Served	X							X[9]		X[9]									X[9]						
AE Review [5]		<==========																							
Concomitant Medication Review		<==========																							
Discharge																									

Procedure [1]	**Day 2**								**Day 3**		**Day 4**
	16 hr	**17 hr**	**19 hr**	**22 hr**	**24 hr**	**28 hr**	**32 hr**	**36 hr**	**48 hr**	**60 hr**	**72 hr**
Admission											
Physical Examination					X			X	X		X
Hema/Chem/ Urinalysis tests											X
Vital signs [2]					X				X		X
12-lead ECG					X				X		X
Cardiac telemetry [3]	==========>										
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X
Neurological Examination					X				X		X
Study Treatment											
Pharmacogenetic Sampling (PGx) [4]	==========>										
Meals Served						X[10]		X[10]	X[10]	X[10]	
AE Review [5]	==========>										
Concomitant Medication Review	==========>										
Discharge											X

1: In this study, baseline is Day -1 and Day 1 pre-dose tests.
2: Vital signs include PR, BPs and temperature.
3: Only 24 hrs following the first dose administration
4: A PGx blood sample will be collected at any time during the study after randomization and provided informed consent for genetic reserch. The participation is optional for each subject.
5: All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified. All AEs will be collected from the start of treatment until the follow-up visit at the time points specified.
6: Physical Examination, Vital signs and 12-lead ECG of 7hr and 14hr time point are to be performed prior to second or third dose.
7: PK blood sampling of 7hr and 14hr time point are to be performed right prior to second or third dose.
8: Neurological Examination of 14hr time point are to be performed prior to third dose.
9: On Day 1, breakfast will be served approximately 2hr after the first dose, lunch will be served between 2 to 3 hr prior to second dose and dinner will be served between 2 to 3 hr prior to third dose.
10: On Day 2-3, meal will be served per unit schedule. Mealtime will be described in SRM.

3. INTRODUCTION

GSK2982772 is a first-in-class highly selective, RIP1 kinase inhibitor being developed for the treatment of inflammatory bowel disease (IBD), plaque psoriasis (PsO), rheumatoid arthritis (RA) and other disease conditions.

3.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of oral doses of TID doses for one day with GSK2982772 in Japanese healthy male subjects. This study is the first administration of GSK2982772 to Japanese.

3.2. Background

GSK2982772 is a first-in-class, highly selective, small molecule inhibitor of RIP1 kinase. RIP1 is a member of the receptor-interacting Ser/Thr kinase family containing an amino-terminal kinase domain, an intermediate domain and a carboxy-terminal death domain. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including TNF family cytokines, ligands for TLR3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis [Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008, Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and Nuclear factor-kappaB (NF-kB)-signalling [Ofengeim, 2013, Humphries, 2015]. With this, an inhibitor of RIP1 kinase activity with GSK2982772 may fill a unique niche in the treatment of inflammatory conditions (eg. PsO, RA and IBD) through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

A range of nonclinical studies have been conducted to support the administration of GSK2982772 to humans [GlaxoSmithKline Document Number 2014N204126_04].

The First Time in Human (FTiH) study which was single (fed and fasted) and repeat dose escalation study (Study 200975) of GSK2982772 in healthy male subjects of predominantly White/Caucasian/European heritage in United Kingdom, 67 subjects were exposed to active treatment. GSK2982772 was well-tolerated up to 120 mg BID for 14 days, with no deaths or other non-fatal SAEs being reported.

The PK of GSK2982772 appeared approximately dose proportional over the single dose range 0.1 to 120 mg. Following14 days of repeat dose administration, the Cmax and AUC(0-t) increased approximately proportionally 20 and 60 mg QD, 60 and 120 mg BID.

There was no evidence of accumulation in any of the dosing regimens and trough plasma concentrations appeared to reach steady state from Day 2. Following oral administration of GSK2982772, the median time to Cmax was between 1.5 and 2.5 hr after attainment of Cmax. GSK2982772 concentrations decline rapidly until about 12 hrs post-dose, with a t1/2 of approximately 2 to 6 hrs. The majority of the systemic exposure to GSK2982772 is observed within the first 12 hrs after administration.

The dose in the FTiH study was capped at 120 mg BID based on exposure margins with the no observable adverse effect limit (NOAEL) in the 28 days repeat dose toxicology study in monkeys (10 mg/kg/day). Subsequently, a 13 week repeat dose toxicity study in monkeys has completed which increased the NOAEL to 30 mg/kg/day which will allow for an approximate 4-fold increase in the safety margins, in terms of systemic exposure to GSK2982772.

Thus, currently the study in non-Japanese (Study 205184) is being conducted to explore administration of higher dose levels than achieved in the FTiH study to support subsequent Phase 2a Proof of Concept (PoC) studies and planned Phase 2b dose range studies in subjects with PsO, RA and UC. Study 205184 includes dosing sessions of 120 mg TID (1 day and 14 days), 240 mg TID (1 day and 14 days) and 360 mg BID (1 day and 14 days), in which all 1-day dosing regimens have been completes and GSK2982772 was tolerated in all 1-days dosing sessions.

Detailed information on the safety and PK of GSK2982772 in human can be found in the Investigators Brochure (IB) for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2982772 may be found in the IB. The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2982772]		
Central nervous system (CNS) effects	**Non-clinical data:** In the 4 week repeat dose Good Laboratory Practice (GLP) toxicology study, CNS findings were observed in 4/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordinated movement, irregular gait, trembling, hunched appearance, and decreased activity. The clinical relevance of these findings in humans is not known. In the 13 and 39 week repeat dose GLP toxicology studies, no CNS findings observed in monkeys at highest dose levels of 100 and 60 mg/kg/day, respectively. The NOAEL for 39 week study was determined at 60 mg/kg/day, which corresponds to a gender-averaged Cmax 23.2 µg/mL and AUC 182 µg·hr/mL in plasma. **Clinical data**: A FTiH study with single ascending and multiple ascending doses has been performed in 67 healthy male subjects to date (Study 200975). See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]. No drug-associated CNS adverse events were identified and no SAEs were reported. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]. In the phase IIa psoriasis study (Study 203167), there was one SAE of death via accidental overdose of Ecstasy/MDMA in a 19 year old male subject who was treated with GSK2982772 60 mg BID or placebo. There was no evidence reported to suggest that this event was a suicide.	**Subject Selection:** • Subjects with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening. **Subject Monitoring:** • Subjects will be monitored for signs of CNS-related effects. • Targeted physical examinations with comprehensive neurological assessments will be conducted at appropriate intervals throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids. **Clinical data:** In the FTiH study (Study 200975), no SAEs were reported. One subject experienced an AE herpes zoster 27 days after receiving with placebo and 42 days after receiving dose with GSK2982772 80 mg. The blinded principal investigator determined this to be drug-related. In the IIa psoriasis study (Study 203167) one subject experienced an AE of herpes zoster on Study Day 9 (either 60 mg BID GSK2982772 or placebo). The blinded investigator considered the AE to be of moderate severity and not related to study drug.	**Subject Selection:** • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for T Spot. TB, HIV, Hepatitis B and C, and excluded from the study if positive. • Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. **Subject Monitoring:** • Subjects will be monitored for signs of infection. • See Individual Safety Stopping Criteria for atypical or opportunistic infections (Section 8.1.4)
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection:** • Attenuated or live vaccines should not be administered to subjects for 30 days prior to the first dose of GSK2982772, during study participation and for five half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (e.g., risk of decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect tovaccinations, including against influenza and pneumococcus.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Respiratory effects	**Non-Clinical data:** In the single dose Safety Cardiovascular and Respiratory Study in monkeys, a decrease in minute volume (minute volume: MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14 days repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (MV) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]. **Clinical data:** In the FTiH study, repeat doses of GSK2982772 up to 120 mg BID were administered 14 days in 36 healthy male subjects. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug associated respiratory-related AEs were identified.	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related AEs. • Vital signs will be monitored during study visits.
Suicidality	GSK2982772 is considered to be a CNS-active drug based on pre-clinical studies. **Clinical data:** In the FTiH study, there have been some reports of lethargy, abnormal dreams and depressed mood. No events of suicidal ideation or behaviour or changes in abnormal behaviour were reported. In the phase IIa psoriasis study (203167), one subject reported suicidal ideation at Day 43 via the Columbia Suicide Severity Rating Scale. This subject informed the investigator that he had similar thoughts prior to joining the study but had no intention of acting on this. The investigator determined the subject was of low risk and allowed the subject to remain in the study.	**Subject Selection:** • Subjects with a current history of Suicidal Ideation and Behaviour (SIB) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, Participants being treated with GSK2982772 should be monitored appropriately and observed closely for SIB or any other unusual changes in behaviour. • Families and caregivers of participants being treated with GSK2982772 should be alerted about the need to monitor participants for the emergence of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		unusual changes in behaviour, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.
Reproductive Toxicity	**Non-Clinical Data:** In the rat embryofetal development study, there were no maternal or developmental toxicity at doses ≤200 mg/kg/day. There were maternal and developmental toxicity at dose of 450 mg/kg/day. In the rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day. There was maternal toxicity at dose of ≥300 mg/kg/day and no tolerability at dose of 600 mg/kg/day.	**Subject Selection:** • Males will be included in this study only if they agree to use highly effective methods of contraception and avoid conception until last visit. **Withdrawal Criteria:** • If a female partner should become pregnant during the study, study medication should be discontinued. She will be followed to determine the outcome of the pregnancy.
Drug Interaction	**Non-Clinical Data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (P-gp) inhibitors were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co-administered with GSK2982772. GSK2982772 is a P-gp substrate and therefore co-administration with concomitant medications that are P-gp inhibitors could increase circulating levels of GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of organic anion transporter 3 (OAT3) substrates. Methotrexate(MTX) is an OAT3 substrate in which GSK2982772 could potentially impair the clearance of MTX. See Section 4.3.6 of GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_04].	**Subject Selection:** • Subjects who are taking concomitant medications known to inhibit P-gp or CYP3A4 will be excluded from the study. **Subject Monitoring:** • Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. • Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.

3.3.2. Benefit Assessment

This study is being conducted in healthy participant with no significant medical history. Subjects will not receive benefit from this study. However, knowledge from this study may contribute to the development of GSK2982772 and may benefit patients in the future.

3.3.3. Overall Benefit: Risk Conclusion

It is considered acceptable to conduct this study in healthy subjects, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical pharmacology unit with access to hospital emergency facilities.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
To assess the safety and tolerability of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Adverse events (AEs) Change in laboratory values (clinical chemistry, haematology and urinalysis), 12-lead ECG and cardiac telemetry, vital signs (blood pressure, pulse rate, and body temperature) Physical examinations, including neurological examinations
To characterise the PK profile of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr (AUC(0-24)) and AUC over each dose interval (i.e. AUC(0-7), AUC(7-14) and AUC(14-24)), maximum observed plasma drug concentration (Cmax) following each dose, time to maximum observed plasma drug concentration (Tmax) following each dose, terminal half-life (t1/2) following the third dose, observed trough plasma drug concentrations (C0, C7, C14 and C24), where data allow

5. STUDY DESIGN

5.1. Overall Design

This study will be a double-blind with respect to subjects, investigators and site staff (with the exception of the unblinded site pharmacist), TID oral doses for one day,

ascending dose, randomized, placebo-controlled, 4-way crossover study, shown as the table below;

Group	N	Period 1	Period 2	Period 3	Period 4
A	3	Placebo, TID	60 mg, TID	120 mg, TID	240 mg, TID
B	3	60 mg, TID	Placebo, TID	120 mg, TID	240 mg, TID
C	3	60 mg, TID	120 mg, TID	Placebo, TID	240 mg, TID
D	3	60 mg, TID	120 mg, TID	240 mg, TID	Placebo, TID

Treatment Groups and Duration:

Screening	Within 30 days prior to the first dose on Day1.
Treatment Period	The study will be comprised of four study periods each at least 7 days in duration with subjects in-house for 4 nights (through 72 hrs after the first dose). During each treatment period, subjects will be admitted to the unit the day before dosing and will be discharged after completion of the 72 hrs post-dose assessments. Each subject will receive oral TID doses of GSK2982772 in each treatment period. For TID dosing, GSK2982772 or placebo will be administered at 0 hr (the first dosing), 7 hr (the second dosing) and 14 hr (the third dosing) on Day 1 in each period. On Day 1, subjects will fast 8hr overnight prior to first dose. A breakfast will be served approximately 2hr after first dose. Lunch and dinner will be served between 2 to 3hr prior to second and third doses, respectively.
Washout Period	Will be at least 7 days between treatment period doses for an individual subject.
Follow-up	At least 7 days, and no greater than 14 days after last study treatment administration. If warranted, additional follow-up visits may be scheduled.

5.2. Number of Subjects

Sufficient Japanese healthy male subjects will be enrolled such that up to 12 subjects complete dosing and critical assessments.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence and start from the period to be replaced at the discretion of the GSK and in consultation with the principal investigator.

5.3. Sentinel Dosing

The doses will be staggered such that for each dose, on Day 1 of Period 1, 2 and 3, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety (AEs, clinical labs, vital signs, 12-Lead ECGs and findings during continuous cardiac telemetry) in the blind judgment of the principal investigator

and GSK Medical Monitor through at least 24 hrs after their third dose on Day 1, the remaining subjects may be randomized to dosing in that period.

5.4. Dose Escalation Decisions

The decision to proceed to the next dose level of GSK2982772 within the study will be made by principal investigator and GSK Medical Monitor per each dosing periods.

Dose escalation decisions will be based on blind data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: all AEs, clinical laboratory values, vital signs, 12-Lead ECG up to Day 4 (at discharge) and findings during continuous cardiac telemetry in the previous dose (Section 8.1.1.).

5.5. Participant and Study Completion

A participant is considered to have completed the study if he has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.6. Scientific Rationale for Study Design

This study will include a placebo control study, to allow for evaluation of AEs attributable to treatment versus those independent of treatment.

In Study 200975, 67 subjects were exposed to active treatment. GSK2982772 was well-tolerated, with no deaths or other non-fatal SAEs being reported. Sentinel dosing approach was taken in Study 200975, where two subjects receive placebo or GSK2982772 on Day 1 and the remaining subjects are dosed after safety evaluation at 24 hrs of preceding two subjects. Since this study is the first study in Japanese subjects, this study adopts a cautious approach including sentinel dosing and will include rigorous safety monitoring to confirm the safety profile prior to dose-escalation of single dose of the next dose strength, which was the same way taken in the past non-Japanese study.

In the 4 week repeat dose nonclinical toxicology studies, neurological related events (uncoordinated movement, irregular gait, trembling, hunched appearance and decreased activity) were observed in some rats and monkeys. On the other hand, in the 13 week repeat dose nonclinical toxicology studies in rats or monkeys, or in the 39 week repeat dose nonclinical toxicology study in monkeys, no neurological-related events were observed in rats or monkeys. There have been some reports of lethargy, abnormal dreams, and depressed mood in Study 200975 (See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]). This study includes neurological exams by considering these findings from Study 200975.

In the currently ongoing non-Japanese healthy volunteer study (Study 205184) being conducted in the United Kingdom (UK), several asymptomatic arthyhmias were detected in 6 out of 25 subjects treated with GSK2982772 or placebo. The study was temporarily

put on hold by GSK to assess the totality of these events. A formal review by the GSK Internal Cardiac Safety Panel, inclusive of both internal and external cardiologists, determined that the arrhythmic events were not likely related to GSK2982772 administration based on the timing and random occurrences of the events, the heterogeneity of the arrhythmias, the length of cardiac monitoring being performed during the study, and no findings in preclinical studies. Subsequently, the protocol was amended to increase the number of placebo subjects to balance randomization between active and placebo to understand the background cardiac patterns of subjects who are enrolled compared to when on treatment. Approval to proceed with the study was received from Medicines and Healthcare products Regulatory Agency (MHRA) on 22 March 2018. Study 200975 and Study 205184 did include telemetry, while the cardiac events related to the study drug were not observed in non-Japanese subkects including Study 205184, Since this study is the first study in Japanese subjects, telemetry will be planed in this study.

GSK2982772 concentrations decline rapidly until about 12 hrs post-dose, with a t1/2 of approximately 2 to 3 hrs. It, therefore, is considered sufficient to allow at least 7 days washout between dosing periods. Also, 7 days follow up after the last dose is considered to be sufficient for safety evaluation.

In the ongoing Study 205184, there are two TID dose regimens of 120 mg TID and 240 mg TID. This study plans also TID dose regimen, which allows to compare the PK between Japanese subjects and non-Japanese subjects in order to support dosing of GSK2982772 in Japanese patient population in the Phase 2b dose ranging studies.

5.7. Dose Justification

The initial starting dose planned is 60 mg TID and the maximum dose is 720 mg/day administered as 240 mg TID, which cover the dose range for the proposed Phase 2b study.

In Study 200975, all of the administered regimens (single dose; 0.1-120 mg, repeat dose; 20 and 60 mg QD, 60 and 120 mg BID for 14 days) appeared to be well tolerated, and no dose limiting AEs or safety findings were observed. There were no clinically significant patterns of abnormal vital sign measurements, physical and neurological examinations, 12-lead ECG and holter ECG changes or clinical laboratory (e.g., hematology, chemistry or urinalysis) findings observed in healthy subjects. There were no deaths or SAEs reported in the study.

Since the target dose per day currently planed in Phase IIb study is 720 mg, the dose regimens in Study 205184 in non-Japanese are 120 mg TID, 240 mg TID and 360 mg BID. For the 360 mg BID dose (single day dosing), one subject exceeded Cmax limit with several other subjects approaching the Cmax limit. In addtion, and the AUC(0-24) at 360 mg was also higher than that predicted but within the limits of stopping criteria. Based on the data in Study 205184, 240 mg TID is considered as the maximum dose in this study.

The predicted mean AUC(0-24) for the highest planned doses in the current study of 240 mg TID (40.2 μg･h/mL) approximates parity with the mean AUC(0-24) observed at the

NOAEL (30 mg/kg/day) in the 13 week repeat dose toxicity study in monkey (48.4 μg·h/mL) and is approximately 1/5th to 1/4th of the mean AUC(0-24) observed at the NOAEL (60 mg/kg/day) in the 39 week repeat dose toxicity study in monkey (182 ug·h/mL). Mean Cmax values for 240 mg TID (3.21 μg/mL) doses are predicted to be 1/4th of the mean Cmax observed at the NOAEL in the 13 week monkey study (12.3 μg/mL) and 1/7th of the mean Cmax at the NOAEL in the 39 week monkey study (23.2 μg/mL). Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_04].

The major circulating metabolite is an N-glucuronide which accounts for approximately 70% of drug related material in plasma. Since glucuronidation is a high capacity clearance mechanism it is unlikely that the kinetics of GSK2982772 will become saturable at the higher doses planned in this study.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 20 to 64 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Healthy as determined by the Investigators based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests, and ECG.

   A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigators in consultation with the GSK Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

   Note: Screened subjects with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigators

Weight

3. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5-24.9 kg/m^2 (inclusive).

Sex

4. Japanese Male

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and until follow up visit.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data
2. Abnormal blood pressure as determined by the investigators
3. Symptomatic herpes zoster within 3 months prior to screening
4. Evidence of active or latent TB as documented by medical history and examination, chest X-rays (anterior and lateral), and TB testing (T Spot. TB)
5. Alanine Aminotransferase (ALT) >1.5x upper limit of normal (ULN)
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
8. History of active infections within 14 days of first receiving study medication.
9. QTcF > 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

- For purposes of data analysis, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

10. History or diagnosis of obstructive sleep apnoea, or a significant respiratory disorder. Childhood asthma that was fully resolved is permitted.
11. History of active Suicidal Ideation Behaviour within the past 6 months or any history of attempted suicide in a participant's lifetime.
12. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.

Prior/Concomitant Therapy

13. Past or intended use of over-the-counter or prescription medication including herbal medications within 14 days prior to dosing.
14. Live vaccine(s) within 1 month prior to screening, or plans to receive such vaccines during the study

Prior/Concurrent Clinical Study Experience

15. History of donation of blood or blood products ≥ 400 mL within 3 months or ≥ 200 mL within 1 month prior to screening
16. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
17. The subject has participated in a other clinical study or other medical research within 4 months prior to the first dosing day in the current study.

Diagnostic assessments

18. The subject is positive Serological test for syphilis (RPR and TP), Tuberculosis, HIV Antigen/Antibody, Hep B surface antigen (HbsAg), Hep C virus (HCV) antibody, or HTLV-1 antibody at screening.
19. Positive pre-study drug screen
20. Regular use of known drugs of abuse

Other Exclusions

21. Regular alcohol consumption within 6 months prior to the study defined as:
    - For an average weekly intake of > 14 units for males. One unit is equivalent to 350 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits
22. Smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening
23. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigators or GSK Medical Monitor, contraindicates participation in the study

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the start of study treatment until follow-up visit.

Once in the clinical unit subjects will not be allowed to eat anything other than the food provided by the study centre.

- Subjects must then fast from all food and drink (except water) for 8 hrs prior to first dose.
- Subjects must then fast from all food and drink (except water) for 8 hrs prior to any clinical laboratory evaluations.
- Water is permitted with dosing and at all times except 1 hr pre-dose through 2 hrs post-dose.
- On Day 1, breakfast will be served approximately 2 hr after first dose. Lunch will be served between 2 to 3 hr prior to second dose. Dinner will be served between 2 to 3 hr prior to third dose. On Day 2-3, meal will be served per unit schedule. Mealtime will be described in SRM.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing period, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hrs before the start of dosing until after collection of the final PK sample.
- During each dosing period, subjects will abstain from alcohol for 24 hrs before the start of dosing until after collection of the final PK sample.
- Use of tobacco, nicotine, or nicotine-containing products (including nicotine patch) will not be allowed from 6-months before screening until after collection of the final PK sample.

6.3.3. Activity

Subjects will abstain from strenuous exercise for 48 hrs prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watching television, read).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure judged ineligible) may not be rescreened.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name	**GSK2982772 30 mg**	**GSK2982772 120 mg**	**Placebo to match GSK2982772 30mg**	**Placebo to match GSK2982772 120mg**
Dosage formulation	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s)	30 mg	120 mg	NA	NA
Route of Administration	Oral	Oral	Oral	Oral
Dosing instructions	As directed	As directed	As directed	As directed
Physical description	White to almost white, round, film-coated tablet	White to almost white, oval, film-coated tablet	White to almost white, round, film-coated tablet	White to almost white, oval, film-coated tablet
Packaging and Labelling	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.
Manufacturer	Aptuit (Italy)	GSK (UK)	Aptuit (Italy)	GSK (UK)

7.2. Method of Treatment Assignment

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 4 groups, according to the randomization schedule generated prior to the study by the Biomedical Data Sciences Department at GSK. Each participant will be dispensed blinded study treatment, labelled with his unique randomization number, throughout the study.

Subjects will be randomized to one of four sequences (A, B, C and D), where the treatments in the sequences are:

- A: Placebo TID / 60 mg TID / 120 mg TID / 240 mg TID
- B: 60 mg TID / Placebo TID / 120 mg TID / 240 mg TID
- C: 60 mg TID / 120 mg TID / Placebo TID / 240 mg TID
- D: 60 mg TID / 120 mg TID / 240 mg TID / Placebo TID

7.3. Blinding

This study will be a double-blind with respect to subjects, investigators and site staff (with the exception of the unblinded site pharmacist).

Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study.

A participant will be withdrawn if the participant's treatment code is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the case report form (CRF).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to principal investigator in accordance with local regulations and/or GSK policy.

7.4. Preparation/Handling/Storage/Accountability

1. The investigators or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants randomized 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 labeled storage conditions with access limited to the investigators and authorized site staff.
3. The investigators, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
    - Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigators, where this is required by local laws, or is available upon request from GSK.

7.5. Treatment Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study treatment directly from the investigators or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The GSK Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigators and GSK, the medication will not interfere with the study.

7.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK, or with GSK2982772, after completion of the study because only healthy subjects are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Dose Stopping Criteria

The decision to proceed to the next dose level of GSK2982772 in each part of this study will be made by the principal investigator and GSK Medical Monitor based on safety results (AEs, clinical labs, vital signs, 12-Lead ECGs and findings during continuous cardiac telemetry) obtained in at least 6 subjects having received active treatment (GSK2982772) at the prior dose level.

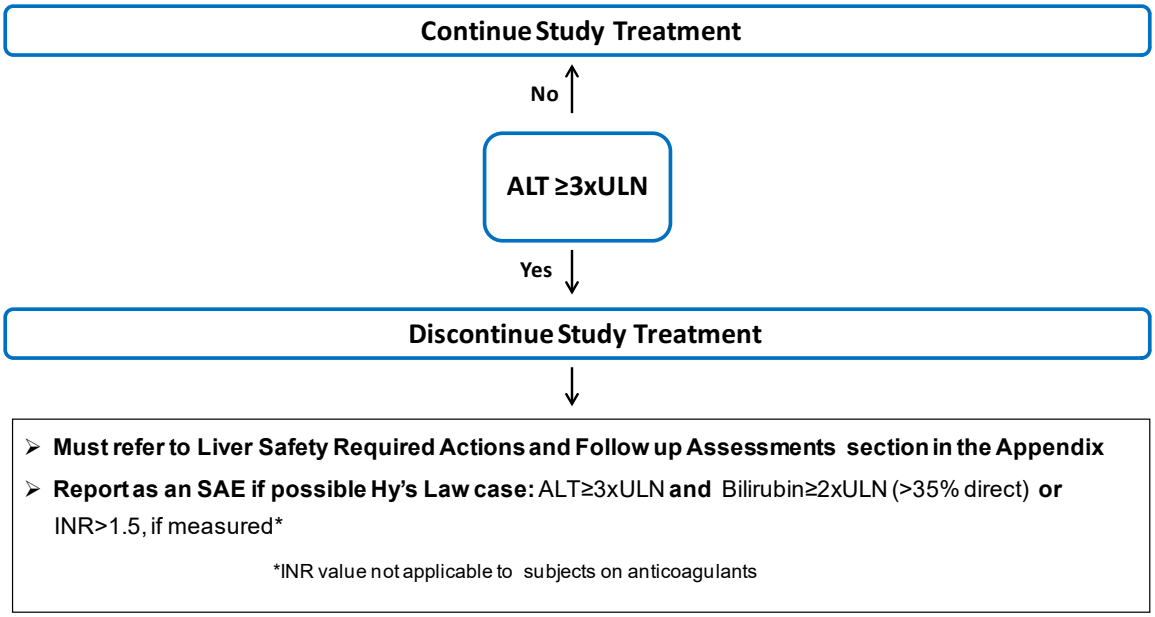
The principal investigator and the GSK Medical Monitor will review the following and dosing will be halted and progression to the next higher dose level stopped if:

- One (1) or more subjects experience a SAE which has a reasonable possibility of relation to study treatment.
- Two (2) or more subjects experience a severe or clinically significant non-serious AE (based upon principal investigator judgment) which has a reasonable possibility of relation to study treatment.
- Two (2) or more subjects experience the same AE of moderate severity which has a reasonable possibility of relation to study treatment.
- Consistent Common Terminology Criteria for Adverse Events (CTCAE) Nervous System AEs of any grade occur across subjects that have a reasonable possibility of relation to study treatment.
- Female partner become pregnant during the treatment period.

8.1.2. Liver Chemistry Stopping Criteria

Study treatment will be discontinued for a participant if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.3. QTc Stopping Criteria

A subject that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.
See Section 9.3.4. about 12-lead ECG.

- QTcF > 500 msec
- QTcF increase > 60 msec from baseline

8.1.4. Individual Safety Stopping Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the principal investigator, after consultation with the GSK Medical Monitor, is possibly, probably or definitely related to investigational product.
- The participant develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (See Section 8.1.2) or QTc stopping criteria (see Section 8.1.3) are met.

8.1.5. Nervous System Stopping Criteria

The CTCAE Nervous System disorder is a monitoring tool which provides the investigators the appropriate guidance for grading of a neurological event. The significance of any neurological event experienced by a subject will be determined based on clinical judgment, characteristics of the event and/or based upon changes from a baseline assessment.

The principal investigator and the GSK Medical Monitor will review all neurological events utilizing the CTCAE Nervous System disorder criteria and dosing may be halted if and progression to the next higher dose level stopped as per Section 8.1.1.

A subject will be withdrawn from the study if:

- A Grade 3 or greater CTCAE Nervous System disorder finding is observed or a significant neurologic change from a subject's baseline physical examination is observed.
- Any adverse event included in the CTCAE for Nervous System disorder, which is also considered to be clinically significant by the principal investigator, will be reviewed for potential subject withdrawal.

Note: Appendix 9 (Section 8.1.1) provides Guidance for Grading AEs that is taken from the CTCAE Version 4.03.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigators for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the GSK may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigators or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the GSK immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The principal investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 400 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigators and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

9.1.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the GSK or designee immediately and under no circumstance should this exceed 24 hrs, as indicated in Appendix 4. The

investigators will submit any updated SAE data to the GSK within 24 hrs of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigators learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigators must promptly notify the GSK.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigators is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non serious AEs of special interest (as defined in Section 3.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.1.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigators to the GSK of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- GSK has a legal responsibility to notify both the local regulatory authority about the safety of a study treatment under clinical investigation. The GSK will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to principal investigator as necessary.
- An principal investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the GSK will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the follow-up visit.

- If a pregnancy is reported, the investigators should inform GSK within 24 hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

For this study, any dose of GSK2982772 greater than 720 mg within a 24-hr time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigators should:

1. Contact the GSK Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days for GSK2982772).
3. Obtain a plasma sample for PK analysis if requested by the GSK Medical Monitor (determined on a case-by-case basis).
4. 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 investigators in consultation with the GSK Medical Monitor based on the clinical evaluation of the participant.

9.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will only be measured and recorded on screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.2. Neurological Examinations

Neurological examination will include, at a minimum, assessment of: mental status, gait, balance, coordination, cranial nerves, motor power, reflexes, and sensory system (light touch and pain). Assessments will be standardized across all scheduled time points (see SoA). Significant changes from the baseline or any clinically significant changes will be noted as part of further scheduled examinations or unscheduled examinations (if needed).

Clinically significant abnormalities or changes in status from baseline will be:

- entered as an adverse event,
- may trigger increased monitoring of the subject(s),
- may result in withdrawal of the subject (see Section 8.2),
- may result in referral to a specialist.

9.3.3. Vital Signs

- Axillary temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

9.3.4. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.3 for QTc withdrawal criteria and additional QTcF readings that may be necessary.
- Single ECGs will be obtained at each time point.
- If QTcF is appeared the value applied the discontinuation criteria, ECG must be conducted two additional readings and be confirmed whether apply the discontinuation criteria.
- Continuous cardiac telemetry will be performed at time points indicated in the SoA (see Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the subject’s source documents.

9.3.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigators must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigators to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigators or GSK Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigators, the etiology should be identified and the GSK notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual of study site and the SoA.

9.3.6. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There is some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some subjects. Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Participants being treated with GSK2982772 should be monitored appropriately and observed closely for SIB or any other unusual changes in behaviour. All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

Families of participants being treated with GSK2982772 should be alerted about the need to monitor participants for the emergence of unusual changes in behaviour, as well as the emergence of SIB and to report such symptoms immediately to the study investigators.

9.4. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2982772 as specified in the SoA. Instructions for the collection and handling of biological samples will be described in the SRM. The actual date and time (24-hr clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK2982772. Samples collected for analyses of GSK2982772 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.5. Genetics

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese ethical guidelines for human genome/gene analysis research.

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

10. STATISTICAL CONSIDERATIONS

The objectives of this study are to evaluate safety, tolerability and PK of GSK2982772 in healthy Japanese subjects. No formal statistical hypotheses will be tested. Descriptive statistics will be used to assess safety and tolerability. An estimation approach will be used to address the pharmacokinetic study objectives, where point estimates and corresponding confidence intervals (CI) will be constructed.

10.1. Sample Size Determination

In a 4-way crossover design, total 12 subjects will be randomized in four groups with a randomization ratio of 1:1:1:1; 3 subjects in each group. The sample size for this study is based on the feasibility rather than statistical considerations. The number of subjects who will take a placebo, 60 mg, 120 mg, or 240 mg dose will be 12 with totalizing four groups. No calculations for formal power and sample size are performed.

One of the objectives of this study is safety, where a number of safety events are of interest. A maximum of 12 subjects will receive each active dose and; therefore, if 0/12 of a particular safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 26.5% could not be ruled out. Whereas if 1/12 of the same safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 38.5% could not be ruled out.

Using a Bayesian approach to determine the CI around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 12 then the posterior distribution would be Beta (2, 12), as outlined in Figure 1. Thus, we can 95% certain that the true probability of the safety event lies between 0.02 and 0.36.

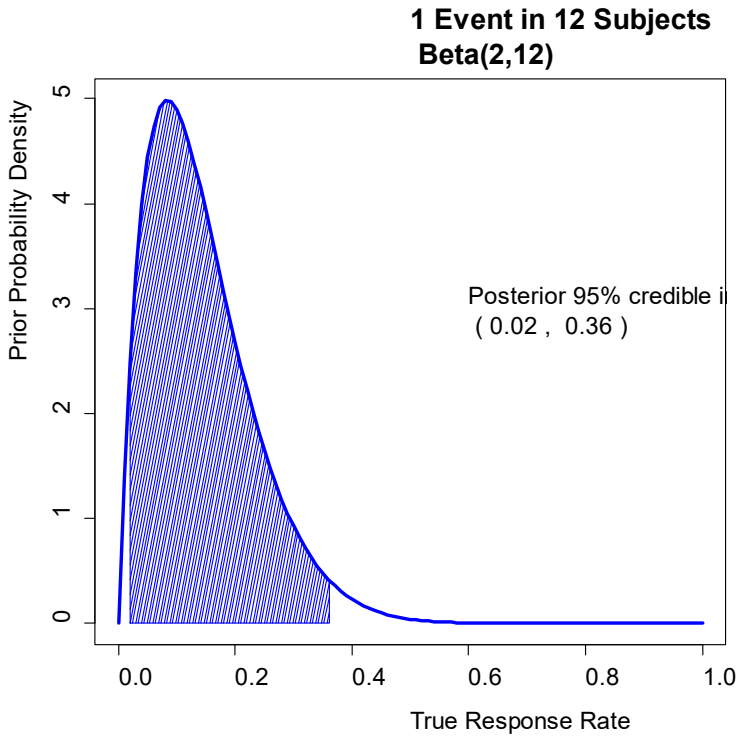


Figure 1 Bayesian Approach to Determine Confidence in Safety Event

Between-subject variability of Cmax and AUC(0-t) of GSK2982772 is estimated to be 32.9% (CV%) and 23.5% (CV%), respectively (based on PK results of 60 mg BID on Day 1 and 120 mg BID on Day1 from Study 200975 Part B). Based on these variability estimates and the sample size of 12, the upper limit value of 95% CI of geometric mean of Cmax and AUC(0-t) is estimated to be approximately 22.6% and 15.9%, respectively.

10.2. Sample Size Sensitivity

Different safety event rates were investigated for sample size sensitivity analysis. If the number of subjects who completed each active dose was different, then the true incidence rates of safety events that could not be ruled out would change. These changes are outlined as below.

Completed N	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
12	2	48.4%
	3	57.2%
	4	65.1%
11	0	28.5%
	1	41.3%
	2	51.8%
	3	61.0%
10	0	30.8%
	1	44.5%
	2	55.6%
	3	65.2%

Following table shows how the results could have variabilities with changing between-subject estimates of variability (CV%) and number of subjects. Estimates of the upper limit values of 95% CI of geometric mean are described using proportions (%) of variability to geometric mean of PK parameters.

N	Estimate of between-subject variability (CV%)			
	20	30	40	50
11	14.2%	21.8%	29.5%	37.3%
12	13.4%	20.5%	27.7%	35.0%
13	12.7%	19.4%	26.2%	33.0%
14	12.1%	18.4%	24.9%	31.4%

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All subjects who have a screening visit will be included.
Enrolled	All subjects who passed screening and entered the study will be included. Note screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.

Population	Description
Safety analyses	All subjects who have received at least one dose of study treatment will be included. This population will be used for the safety analyses.
PK analyses	All subjects in the Safety population for whom a PK sample has been obtained and analyzed will be included. This population will be used for the PK analyses.

10.4. Statistical Analyses

10.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

The tables, figures, and listings will use the Safety Population unless otherwise specified. AEs, changes in clinical laboratory values, 12-Lead ECGs, findings during continuous cardiac telemetry and vital signs will be summarized by dose group (i.e. placebo, 60 mg, 120 mg, and 240 mg) to assess the safety and tolerability of GSK2982772. The safety and tolerability results will not to be formally compared between each group and comparison with placebo will be based on review of descriptive summaries.

10.4.2. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population.

Statistical Analysis Methods

Plasma GSK2982772 concentration-time data will be analysed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following PK parameters will be determined, as data permit: AUC(0-24), AUC(0-7), AUC(7-14) and AUC(14-24), Cmax following each dose, time to maximum observed plasma drug concentration (Tmax) following each dose,t1/2 following the third dose, observed trough plasma concentrations (C0, C7, C14 and C24).

PK data will be presented in graphical and/or tabular form and will be summarised descriptively.

Listings will be generated and summary statistics (n, arithmetic mean with associated 95% CI, standard deviation (SD), minimum, median, maximum, geometric mean with associated 95% CI, SD on log-scale and %CVb) will be calculated for each derived plasma PK parameter for each dose.

The PK-dose relationship will be examined graphically by plotting derived plasma PK parameters for each dose group. Dose proportionality for AUC(0-24), AUC(0-7) and Cmax following the first dose will be assessed by using a power model as described below:

$\log_e$ (PK parameter) = $\mu + S_i + \beta * \log_e (D_j) + \varepsilon_{ij}$

where μ is the intercept, β is the slope, S_i is the random effect for subject i, D_j is the dose (j = 60 mg, 120 mg, or 240 mg), ε_{ij} is the random error. Point estimates for the slope of PK parameters and their associated 90% CI will be presented.

10.4.3. Interim Analyses

A review of safety data will be conducted at the end of each period.

The decision to proceed to higher dose strengths will be made by principal investigator and GSK's Medical Monitor based on assessment of safety and tolerability at the preceding dose. This review can include individual subject data.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADL	Activities of daily life
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
AUC	Area under concentration-time curve
AUC(0-7)	Area under the concentration-time curve from time 0 to 7 hr
AUC(7-14)	Area under the concentration-time curve from time 7 to 14 hr
AUC(14-24)	Area under the concentration-time curve from time 14 to 24 hr
AUC(0-t)	Area under the concentration-time curve from time 0 to the time of the last measurable drug concentration
AUC(0-∞)	Area under the concentration-time curve from time 0 to infinity
BID	Bis in die
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulation
CI	Confidence interval
Cmax	Maximum observed plasma drug concentration
C0	Plasma drug concetration at pre-dose
C7	Plasma drug concetration at 7 hr after dosing
C14	Plasma drug concetration at 14 hr after dosing
C24	Plasma drug concetration at 24 hr after dosing
CNS	Central nervous system
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTN	Clinical Trial Notification
CV	Coefficient of variance
CYP	Cytochrome P450
DAMP	Damage associated molecular pattern
e.g.	Exempli gratia
ECG	Electrocardiogram
FLAIR	FLuid-Attenuated Inversion Recovery
FTiH	First Time in Human
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h/hr(s)	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
Hep B	Hepatitis B

Hep C	Hepatitis C
HIV	Human immunodeficiency virus
HTLV-1	Human T-cell leulemia virus type 1
i.e.	id est
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
kg	Kilogram
loge	Natural logarithm
µg	Micrograms
mg	Milligrams
min	Minute
mL	Milliliter
msec	Milliseconds
MV	Minute volume
MTX	Methotrexate
m^2	Square metre
NA	Not applicable
ng	Nanograms
nL	Nanoliter
NOS	Not otherwise specified
NOAEL	No Observable Adverse Effect Level
OAT3	Organic anion transporter 3
P-gp	P-glycoprotein
pH	Pondus Hydrogenii
PK	Pharmacokinetics
PsO	Psoriasis
PR	Pulse rate
QD	Quaque die
RA	Rheumatoid arthritis
RIP1	Receptor-interacting serine/threonine protein-1
RNA	Ribonucleic acid
RPR	Rapid Plasma Reagin
SAE	Serious adverse event
SAS	Subarachnoid space
SD	Standard deviation
Ser	Serine
SIB	Suicidal Ideation and Behaviour
SoA	Schedule of Activities
SRM	Study Reference Manual

$t_{1/2}$	Terminal half-life
TB	Tuberculosis
Thr	Threonine
TID	Ter in die
T_{max}	Time to maximum observed drug concentration
TNF(α)	Tumour necrosis factor (α)
TNFR1	Tumour necrosis factor receptor-1
TP	Treponema pallidum
UC	Ulcerative colitis
ULN	Upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH ‰Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Uric acid	TG	Total Cholesterol	LDL-cholesterol
	HDL-cholesterol	LDH	GGT	CK (CPK)
	Amylase	Chloride	Phosphorus	CRP
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine drug screen (to include at minimum: Phencyclidines [PCP], Benzodiazepines [BZO], Cocaine [COC], Amphetamines [AMP], Tetrahydrocannabinol [THC], Opiates [OPI], Barbiturates [BAR], Trycyclic antidepressants [TCA]) • Serology (Syphilis [RPR & TP], TB, HIV antigen/antibody, HTLV-1 antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (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).

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the GSK with sufficient, accurate financial information as requested to allow the GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who received rescreening must be re-consented the ICF(s).
- The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the GSK. Any participant records or datasets that are transferred to the GSK will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the GSK, by appropriate IRB members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the GSK before submission. This allows the GSK to protect proprietary information and to provide comments.

- The GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the GSK will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- 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.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the GSK or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The GSK or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional

policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the GSK. No records may be transferred to another location or party without written notification to the GSK.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the list of the source documents.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the GSK or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the GSK's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• 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 participant'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 participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity • 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 with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include 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.

Recording AE and SAE

AE 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) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 24 hrs of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hrs. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hrs of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form. • Contacts for SAE reporting can be found in Appendix 8.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **GSK Medical Monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Appendix 8.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of < 1% per year as described in Table 2 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- In addition male participants must refrain from donating sperm for duration of study and until follow up visit

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the Women of Childbearing Potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the*

preferred and usual lifestyle of the participant.)

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and until follow up visit.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will discontinue study treatment and attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hrs 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.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2982772 or immuno-inflammatory and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2982772 or study treatments of this drug class, and immuno-inflammatory diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed for UDP-glucuronosyltransferase 1-9 family, polypeptide A cluster enzyme that is encoded by the UGT1A9 gene complex. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2982772 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- Samples will be given a code and stored securely.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2982772 (or study treatments of this class) continues but no longer than 15 years after the last subject last visit or other period as per local requirements.
- If particinpant chooses to stop the pharmacogenetics part of the study after giving a sample, GSK will not conduct any new tests on the sample. GSK will destroy the sample. GSK will keep and use any results generated before you stopped participating in the pharmacogenetics study.
- GSK will only use the coded results to verify or show the quality of analyses that have already been reported. GSK will take steps to ensure that your coded results are not used in any new analyses. If new analyses are conducted then GSK will make sure that the subject's number will be deleted.
- GSK may provide your genetic information generated from your sample for research with other companies or universities to learn more about other medicines, this immuno-inflammatory disease and other disease, only by deleting the subject number before it is provided, so that provided information will not be identified in any way and your privacy is protected.

- If GSK decides to use your sample and/or your genetic information for a different study, GSK will ask participant for his permission again or GSK will ask an adequate committee to review the study from ethical standpoint.

12.7. Appendix 7: Liver Safety Required Actions and Follow up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 3xULN

If ALT ≥ 3xULN AND bilirubin[1,2] ≥ 2xULN (> 35% direct bilirubin) or INR > 1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hrs
• 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, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR > 1.5

• 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, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT ≥ 3xULN AND bilirubin < 2xULN and INR ≤ 1.5:</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain plasma sample for pharmacokinetic (PK) analysis, obtained within 24 hrs of last dose[4]
• 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

If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR > 1.5:</td></tr>
</table>

Liver Chemistry Stopping 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	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • 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. Includes: Hepatitis A immunoglobulin M (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)
4. 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 PK 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.

12.8. Appendix 8: Country-specific requirements

12.8.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (Ministry of Health and Welfare (MHW) Notification No.28 dated 27th March, 1997)" and the Pharmaceuticals and Medical Devices Act.

GSK will submit the Clinical Trial Notification (CTN) to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

12.8.2. Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential participant of the study including the written information. The investigator (or subinvestigator) should provide the participant ample time and opportunity to inquire about details of the study. The participant should sign and personally date the consent form. The participant may consider the content of the written information at home. The person, who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the participant.

12.8.3. Study Period

JUL 2018 - SEP 2018

12.8.4. Study Administrative Structure

Sponsor Legal Registered Address:

GlaxoSmithKline K.K. (GSK)
Akasaka Intercity AIR, 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
Study Director: PPD Head, Medicines Development, Clinical Pharmacology & Science Promotion Office

Sponsor Contact Address:

Lead Author:
PPD Manager, Medicines Development, Clinical Pharmacology & Science Promotion Office

Sponsor's Emergency Contact Information (10:00-18:00, Monday to Friday, except national holidays and year-end and new-year holidays);

Medicines Development (Clinical Pharmacology), GlaxoSmithKline K.K.
TEL: PPD (direct dialling)
FAX: PPD

Contact Information at Night and on Holidays (Monday to Friday: 18:00-10:00, Saturday, Sunday, national holidays, year-end and new-year holidays)
PPD (mobile: PPD

GSK Medical Monitor / Contact Address for SAE

PPD
GlaxoSmithKline K.K. (GSK)
Akasaka Intercity AIR, 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
TEL: PPD (mobile)／PPD (direct dialling)
FAX: PPD

Medical Institution and Investigator

PPD
SOUSEIKAI Hakata Clinic
6-18 Tenyamatchi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

Laboratories

Clinical Laboratory (except HTLV-1 serology and TB)
SOUSEIKAI Hakata Clinic
Person in charge: PPD
6-18 Tenyamachi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

HTLV-1 serology and TB (If subject meet Liver chemistry stopping criteria, include anti-nuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins, and viral hepatitis serology described in Appendix 7, but except HBsAg)
Person in charge: PPD
LSI Medience Inc.
30-1 Shimura 3-chome, Itabashi-ku, Tokyo 174-8555, Japan
TEL: PPD
FAX: PPD

Pharmacokinetics Measurement Facilities
Covance Laboratories Limited
Person in charge: PPD
Otley Road, Harrogate, North Yorkshire, HG3 1PY, UK
TEL: PPD

Gx Research Administration (Sample Management , Sample Storage Facility, DNA Extraction Facility)
Contact person: PPD
Q2 Solutions
Q Squared Solutions (Quest) LLC
27027 Tourney Road, Suite 2E
Valencia, CA 91355
USA
TEL: PPD
FAX: PPD

Contract research organization

Role: Study Monitoring
Person in charge (Monitor Leader): PPD
Mediscience Planning Inc.
2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Protocol & Informed Consent Form)
Person in charge: PPD
Mediscience Planning Inc.
2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Clinical Study Report)
Person in charge: PPD
Mediscience Planning Inc.
2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Pharmacokineic Parameter Derivation
Person in charge: PPD
Mediscience Planning Inc.
1-2-1 Nihonbashi hamacho, Chuo-ku, Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

Role: Data Loading
Person in charge: PPD
Mediscience Planning Inc.
1-2-1 Nihonbashi hamacho, Chuo-ku, Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

12.9. Appendix 9: Nervous System Adverse Events (CTCAE Criteria)

Taken from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

The purpose of this Appendix is to provide guidance and is to be used in conjunction with the Investigator's judgment.

Table 3 Guidance For Grading Adverse Events

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental Activities of daily life (ADL)	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-	A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-	A disorder characterized by systematic and extensive loss of memory.
Aphonia	-	-	Voicelessness; unable to speak	-	-	A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-	A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-	A disorder characterized by a conspicuous change in cognitive function.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-	A disorder characterized by a deterioration in the ability to concentrate.
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death	A disorder characterized by a decrease in ability to perceive and respond.
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-	A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-	A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-	A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-	A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention		A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
				indicated		
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a pathologic process involving the brain.
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by a reduction in the strength of the facial muscles.
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the facial nerve (seventh cranial nerve).
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention	Death	A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
	indicated			indicated		
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-	A disorder characterized by characterized by excessive sleepiness during the daytime.
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, Intracranial Pressure (ICP) monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by bleeding from the cranium.
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-	A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum ± mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum ± moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death	A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-	A disorder characterized by a deterioration in memory function.
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by uncontrolled and purposeless movements.
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by intense painful sensation along a nerve or

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
						group of nerves.
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involuntary movements of the eyeballs.
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the olfactory nerve (first cranial nerve).
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral motor nerves.
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.
Presyncope	-	Present (e.g., near fainting)	-	-	-	A disorder characterized by an episode of lightheadedness and

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
						dizziness which may precede an episode of syncope.
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by paralysis of the recurrent laryngeal nerve.
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by characterized by excessive sleepiness and drowsiness.
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death	A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.
Syncope	-	-	Fainting; orthostatic collapse	-	-	A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-	A disorder characterized by a brief attack (less than 24 hrs) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	-

12.10. Appendix 10: Protocol Amendment History

Not applicable

TITLE PAGE

Protocol Title: A single-centre, randomized, double-blind, dose-ascending, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of oral TID doses (one day) of GSK2982772 in Japanese healthy male subjects

Protocol Number: 205037

Short Title: Phase I study of GSK2982772 in Japanese healthy male subjects

Compound Number: GSK2982772

Sponsor Name and Legal Registered Address:

GlaxoSmithKline K.K. (GSK)
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Regulatory Agency Identifying Number(s): Not applicable

Approval Date: 27-JUN-2018

SPONSOR SIGNATORY:

Kosuke Kozaiwa VP & Head of Medicines Development Development & Medical Affairs GlaxoSmithKline K.K.	**Date**

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1. SYNOPSIS

Protocol Title: A single-centre, randomized, double-blind, dose-ascending, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of oral TID doses (one day) of GSK2982772 in Japanese healthy male subjects

Short Title: Phase I study of GSK2982772 in Japanese healthy male subjects

Rationale:

This study is the first administration of GSK2982772 to Japanese. The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of oral doses of TID doses for one day with GSK2982772 in Japanese healthy male subjects. GSK2982772 or placebo will be administered at 0 hr (the first dosing), 7 hr (the second dosing) and 14 hr (the third dosing) on Day 1 in each period. The intention of this study is to provide sufficient confidence in the safety of the molecule to inform progression to further repeat dose studies in patients. The dose range proposed in this study is based on a low starting dose escalating to the highest dose that is intended for the Phase 2b dose range study.

Objectives and Endpoints:

Objectives	Endpoints
To assess the safety and tolerability of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Adverse events (AEs) Change in laboratory values (clinical chemistry, haematology and urinalysis), 12-lead ECG and cardiac telemetry, vital signs (blood pressure, pulse rate, and body temperature) Physical examinations, including neurological examinations
To characterise the PK profile of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr (AUC(0-24)) and AUC over each dose interval (i.e. AUC(0-7), AUC(7-14) and AUC(14-24)), maximum observed plasma drug concentration (Cmax) following each dose, time to maximum observed plasma drug concentration (Tmax) following each dose, terminal half-life (t1/2) following the third dose, observed trough plasma drug concentrations (C0, C7, C14 and C24), where data allow

Overall Design:

This study will be a double-blind with respect to subjects, investigators and site staff (with the exception of the unblinded site pharmacist), TID oral doses for one day,

ascending dose, randomized, placebo-controlled, 4-way crossover study, shown as the table below;

Group	N	Period 1	Period 2	Period 3	Period 4
A	3	Placebo, TID	60 mg, TID	120 mg, TID	240 mg, TID
B	3	60 mg, TID	Placebo, TID	120 mg, TID	240 mg, TID
C	3	60 mg, TID	120 mg, TID	Placebo, TID	240 mg, TID
D	3	60 mg, TID	120 mg, TID	240 mg, TID	Placebo, TID

Number of Participants:

Sufficient Japanese healthy male subjects will be enrolled such that up to approximately 12 subjects complete dosing and critical assessments.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence and start from the period to be replaced at the discretion of the GSK and in consultation with the principal investigator.

Sentinel Dosing:

The doses will be staggered such that for each dose, on Day 1 of Period 1, 2 and 3, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety (AEs, clinical labs, vital signs, 12-Lead ECGs and Cardiac telemetry) in the judgment of the principal investigator and GSK Medical Monitor through at least 24 hrs after their third dose on Day 1, the remaining subjects may be randomized to dosing in that period.

Treatment Groups and Duration:

Screening	Within 30 days prior to the first dose on Day1.
Treatment Period	The study will be comprised of four study periods each at least 7 days in duration with subjects in-house for 4 nights (through 72 hrs after the first dose). During each treatment period, subjects will be admitted to the unit the day before dosing and will be discharged after completion of the 72 hrs post-dose assessments. Each subject will receive oral TID doses of GSK2982772 in each treatment period. For TID dosing, GSK2982772 or placebo will be administered at 0 hr (the first dosing), 7 hr (the second dosing) and 14 hr (the third dosing) on Day 1 in each period. On Day 1, subjects will fast 8hr overnight prior to first dose. A breakfast will be served approximately 2hr after first dose. Lunch and dinner will be served between 2 to 3hr prior to second and third doses, respectively.
Washout Period	Will be at least 7 days between treatment period doses for an individual

	subject.
Follow-up	At least 7 days, and no greater than 14 days after last study treatment administration. If warranted, additional follow-up visits may be scheduled.

2. SCHEDULE OF ACTIVITIES (SoA)

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 Schedule of Activities (SoA) tables, are essential and required for study conduct.

The Study Reference Manual (SRM) will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA tables.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

Time and Events Table for Screening and Follow-up Assessments

Procedure	**Screening[1]**	**Follow-up Visit[2]**	***Notes***
Outpatient Visit	X	X	
Informed Consent	X		
Medical/medication/drug /alcohol history	X		
Demographics	X		
Physical Examination	X	X	*Additional examinations may be performed, by the Investigators, as deemed necessary.*
Drug screen	X		*Additional tests may be performed by the Investigators, as deemed necessary. Tests will be conducted within site specified standards.*
Syphilis, Human immunodeficiency virus (HIV), Human T-cell leulemia virus type 1 (HTLV-1), Hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Tuberculosis (TB) Test	X		Conducted at the standard practice of the site.
X-ray Test	X		Anterior & lateral chest X-ray will be taken.
Hema/Chem/Urinalysis tests	X	X	
Height and weight	X		
12-lead ECG and vital signs	X	X	*Vital signs to include pulse rate (PR), blood pressure (BPs) and temperature.*
AE Review	X	X	*All Serious Adverse Effects (SAEs) will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified. All AEs will be collected from the start of treatment until the follow-up visit at the time points specified.*
Concomitant Medication Review	X	X	

1: Within 30 days prior to the first dosing

2: Follow-up Visit to occur at least 7 days, and no greater than 14 days after last study treatment administration. If a participant withdrew from the study after received GSK2982772 or placebo dose, the safety assessments listed at follow-up visit will be required.

Detailed Time and Events Table for Days 1-4 (common Period1-4)

Procedure [1]	Day -1	Day 1																							
		Pre-dose	0	20 min	40 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	7 hr	7 hr 20 min	7 hr 40 min	8 hr	8.5 hr	9 hr	10 hr	11 hr	12 hr	14 hr	14 hr 20 min	14 hr 40 min	15 hr	15.5 hr
Admission	X																								
Physical Examination	X	X						X				X[6]									X[6]				
Hema/Chem/ Urinalysis tests	X																								
Vital signs [2]		X						X				X[6]									X[6]				
12-lead ECG		X						X				X[6]									X[6]				
Cardiac telemetry [3]			<==========																						
PK blood sampling		X		X	X	X	X	X	X		X	X[7]	X	X	X	X	X	X		X	X[7]	X	X	X	X
Neurological Examination	X							X									X				X[8]				
Study Treatment			X									X									X				
Pharmacogenetic Sampling (PGx) [4]			<==========																						
Meals Served	X							X[9]		X[9]									X[9]						
AE Review [5]		<==========																							
Concomitant Medication Review		<==========																							
Discharge																									

Procedure [1]	**Day 2**								**Day 3**		**Day 4**
	16 hr	**17 hr**	**19 hr**	**22 hr**	**24 hr**	**28 hr**	**32 hr**	**36 hr**	**48 hr**	**60 hr**	**72 hr**
Admission											
Physical Examination					X			X	X		X
Hema/Chem/ Urinalysis tests											X
Vital signs [2]					X				X		X
12-lead ECG					X				X		X
Cardiac telemetry [3]	==========>										
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X
Neurological Examination					X				X		X
Study Treatment											
Pharmacogenetic Sampling (PGx) [4]	==========>										
Meals Served						X[10]		X[10]	X[10]	X[10]	
AE Review [5]	==========>										
Concomitant Medication Review	==========>										
Discharge											X

1: In this study, baseline is Day -1 and Day 1 pre-dose tests.
2: Vital signs include PR, BPs and temperature.
3: Only 24 hrs following the first dose administration
4: A PGx blood sample will be collected at any time during the study after randomization and provided informed consent for genetic reserch. The participation is optional for each subject.
5: All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified. All AEs will be collected from the start of treatment until the follow-up visit at the time points specified.
6: Physical Examination, Vital signs and 12-lead ECG of 7hr and 14hr time point are to be performed prior to second or third dose.
7: PK blood sampling of 7hr and 14hr time point are to be performed right prior to second or third dose.
8: Neurological Examination of 14hr time point are to be performed prior to third dose.
9: On Day 1, breakfast will be served approximately 2hr after the first dose, lunch will be served between 2 to 3 hr prior to second dose and dinner will be served between 2 to 3 hr prior to third dose.
10: On Day 2-3, meal will be served per unit schedule. Mealtime will be described in SRM.

3. INTRODUCTION

GSK2982772 is a first-in-class highly selective, RIP1 kinase inhibitor being developed for the treatment of inflammatory bowel disease (IBD), plaque psoriasis (PsO), rheumatoid arthritis (RA) and other disease conditions.

3.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of oral doses of TID doses for one day with GSK2982772 in Japanese healthy male subjects. This study is the first administration of GSK2982772 to Japanese.

3.2. Background

GSK2982772 is a first-in-class, highly selective, small molecule inhibitor of RIP1 kinase. RIP1 is a member of the receptor-interacting Ser/Thr kinase family containing an amino-terminal kinase domain, an intermediate domain and a carboxy-terminal death domain. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including TNF family cytokines, ligands for TLR3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis [Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008, Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and Nuclear factor-kappaB (NF-kB)-signalling [Ofengeim, 2013, Humphries, 2015]. With this, an inhibitor of RIP1 kinase activity with GSK2982772 may fill a unique niche in the treatment of inflammatory conditions (eg. PsO, RA and IBD) through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

A range of nonclinical studies have been conducted to support the administration of GSK2982772 to humans [GlaxoSmithKline Document Number 2014N204126_04].

The First Time in Human (FTiH) study which was single (fed and fasted) and repeat dose escalation study (Study 200975) of GSK2982772 in healthy male subjects of predominantly White/Caucasian/European heritage in United Kingdom, 67 subjects were exposed to active treatment. GSK2982772 was well-tolerated up to 120 mg BID for 14 days, with no deaths or other non-fatal SAEs being reported.

The PK of GSK2982772 appeared approximately dose proportional over the single dose range 0.1 to 120 mg. Following14 days of repeat dose administration, the Cmax and AUC(0-t) increased approximately proportionally 20 and 60 mg QD, 60 and 120 mg BID.

There was no evidence of accumulation in any of the dosing regimens and trough plasma concentrations appeared to reach steady state from Day 2. Following oral administration of GSK2982772, the median time to Cmax was between 1.5 and 2.5 hr after attainment of Cmax. GSK2982772 concentrations decline rapidly until about 12 hrs post-dose, with a t1/2 of approximately 2 to 6 hrs. The majority of the systemic exposure to GSK2982772 is observed within the first 12 hrs after administration.

The dose in the FTiH study was capped at 120 mg BID based on exposure margins with the no observable adverse effect limit (NOAEL) in the 28 days repeat dose toxicology study in monkeys (10 mg/kg/day). Subsequently, a 13 week repeat dose toxicity study in monkeys has completed which increased the NOAEL to 30 mg/kg/day which will allow for an approximate 4-fold increase in the safety margins, in terms of systemic exposure to GSK2982772.

Thus, currently the study in non-Japanese (Study 205184) is being conducted to explore administration of higher dose levels than achieved in the FTiH study to support subsequent Phase 2a Proof of Concept (PoC) studies and planned Phase 2b dose range studies in subjects with PsO, RA and UC. Study 205184 includes dosing sessions of 120 mg TID (1 day and 14 days), 240 mg TID (1 day and 14 days) and 360 mg BID (1 day and 14 days), in which all 1-day dosing regimens have been completes and GSK2982772 was tolerated in all 1-days dosing sessions.

Detailed information on the safety and PK of GSK2982772 in human can be found in the Investigators Brochure (IB) for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2982772 may be found in the IB. The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2982772]		
Central nervous systemCNS) effects	**Non-clinical data:** In the 4 week repeat dose Good Laboratory Practice (GLP) toxicology study, CNS findings were observed in 4/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordinated movement, irregular gait, trembling, hunched appearance, and decreased activity. The clinical relevance of these findings in humans is not known. In the 13 and 39 week repeat dose GLP toxicology studies, no CNS findings observed in monkeys at highest dose levels of 100 and 60 mg/kg/day, respectively. The NOAEL for 39 week study was determined at 60 mg/kg/day, which corresponds to a gender-averaged Cmax 23.2 µg/mL and AUC 182 µg·hr/mL in plasma. **Clinical data**: A FTiH study with single ascending and multiple ascending doses has been performed in 67 healthy male subjects to date (Study 200975). See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]. No drug-associated CNS adverse events were identified and no SAEs were reported. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]. In the phase IIa psoriasis study (Study 203167), there was one SAE of death via accidental overdose of Ecstasy/MDMA in a 19 year old male subject who was treated with GSK2982772 60 mg BID or placebo. There was no evidence reported to suggest that this event was a suicide.	**Subject Selection:** • Subjects with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at screening. **Subject Monitoring:** • Subjects will be monitored for signs of CNS-related effects. • Targeted physical examinations with comprehensive neurological assessments will be conducted at appropriate intervals throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids. **Clinical data:** In the FTiH study (Study 200975), no SAEs were reported. One subject experienced an AE herpes zoster 27 days after receiving with placebo and 42 days after receiving dose with GSK2982772 80 mg. The blinded principal investigator determined this to be drug-related. In the IIa psoriasis study (Study 203167) one subject experienced an AE of herpes zoster on Study Day 9 (either 60 mg BID GSK2982772 or placebo). The blinded investigator considered the AE to be of moderate severity and not related to study drug.	**Subject Selection:** • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for T Spot. TB, HIV, Hepatitis B and C, and excluded from the study if positive. • Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. **Subject Monitoring:** • Subjects will be monitored for signs of infection. • See Individual Safety Stopping Criteria for atypical or opportunistic infections (Section 8.1.4)
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	**Subject Selection:** • Attenuated or live vaccines should not be administered to subjects for 30 days prior to the first dose of GSK2982772, during study participation and for five half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit:risk (e.g., risk of decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect tovaccinations, including against influenza and pneumococcus.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Respiratory effects	**Non-Clinical data:** In the single dose Safety Cardiovascular and Respiratory Study in monkeys, a decrease in minute volume (minute volume: MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14 days repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (MV) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]. **Clinical data:** In the FTiH study, repeat doses of GSK2982772 up to 120 mg BID were administered 14 days in 36 healthy male subjects. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug associated respiratory-related AEs were identified.	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related AEs. • Vital signs will be monitored during study visits.
Suicidality	GSK2982772 is considered to be a CNS-active drug based on pre-clinical studies. **Clinical data:** In the FTiH study, there have been some reports of lethargy, abnormal dreams and depressed mood. No events of suicidal ideation or behaviour or changes in abnormal behaviour were reported. In the phase IIa psoriasis study (203167), one subject reported suicidal ideation at Day 43 via the Columbia Suicide Severity Rating Scale. This subject informed the investigator that he had similar thoughts prior to joining the study but had no intention of acting on this. The investigator determined the subject was of low risk and allowed the subject to remain in the study.	**Subject Selection:** • Subjects with a current history of Suicidal Ideation and Behaviour (SIB) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, Participants being treated with GSK2982772 should be monitored appropriately and observed closely for SIB or any other unusual changes in behaviour. • Families and caregivers of participants being treated with GSK2982772 should be alerted about the need to monitor participants for the emergence of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		unusual changes in behaviour, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.
Reproductive Toxicity	**Non-Clinical Data:** In the rat embryofetal development study, there were no maternal or developmental toxicity at doses ≤200 mg/kg/day. There were maternal and developmental toxicity at dose of 450 mg/kg/day. In the rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day. There was maternal toxicity at dose of ≥300 mg/kg/day and no tolerability at dose of 600 mg/kg/day.	**Subject Selection:** • Males will be included in this study only if they agree to use highly effective methods of contraception and avoid conception until last visit. **Withdrawal Criteria:** • If a female partner should become pregnant during the study, study medication should be discontinued. She will be followed to determine the outcome of the pregnancy.
Drug Interaction	**Non-Clinical Data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (P-gp) inhibitors were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co-administered with GSK2982772. GSK2982772 is a P-gp substrate and therefore co-administration with concomitant medications that are P-gp inhibitors could increase circulating levels of GSK2982772. There is a low risk that GSK2982772 could be a perpetrator of organic anion transporter 3 (OAT3) substrates. Methotrexate(MTX) is an OAT3 substrate in which GSK2982772 could potentially impair the clearance of MTX. See Section 4.3.6 of GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_04].	**Subject Selection:** • Subjects who are taking concomitant medications known to inhibit P-gp or CYP3A4 will be excluded from the study. **Subject Monitoring:** • Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. • Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.

3.3.2. Benefit Assessment

This study is being conducted in healthy participant with no significant medical history. Subjects will not receive benefit from this study. However, knowledge from this study may contribute to the development of GSK2982772 and may benefit patients in the future.

3.3.3. Overall Benefit: Risk Conclusion

It is considered acceptable to conduct this study in healthy subjects, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical pharmacology unit with access to hospital emergency facilities.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
To assess the safety and tolerability of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Adverse events (AEs) Change in laboratory values (clinical chemistry, haematology and urinalysis), 12-lead ECG and cardiac telemetry, vital signs (blood pressure, pulse rate, and body temperature) Physical examinations, including neurological examinations
To characterise the PK profile of TID doses for one day of GSK2982772 in Japanese healthy male subjects	Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr (AUC(0-24)) and AUC over each dose interval (i.e. AUC(0-7), AUC(7-14) and AUC(14-24)), maximum observed plasma drug concentration (Cmax) following each dose, time to maximum observed plasma drug concentration (Tmax) following each dose, terminal half-life (t1/2) following the third dose, observed trough plasma drug concentrations (C0, C7, C14 and C24), where data allow

5. STUDY DESIGN

5.1. Overall Design

This study will be a double-blind with respect to subjects, investigators and site staff (with the exception of the unblinded site pharmacist), TID oral doses for one day,

ascending dose, randomized, placebo-controlled, 4-way crossover study, shown as the table below;

Group	N	Period 1	Period 2	Period 3	Period 4
A	3	Placebo, TID	60 mg, TID	120 mg, TID	240 mg, TID
B	3	60 mg, TID	Placebo, TID	120 mg, TID	240 mg, TID
C	3	60 mg, TID	120 mg, TID	Placebo, TID	240 mg, TID
D	3	60 mg, TID	120 mg, TID	240 mg, TID	Placebo, TID

Treatment Groups and Duration:

Screening	Within 30 days prior to the first dose on Day1.
Treatment Period	The study will be comprised of four study periods each at least 7 days in duration with subjects in-house for 4 nights (through 72 hrs after the first dose). During each treatment period, subjects will be admitted to the unit the day before dosing and will be discharged after completion of the 72 hrs post-dose assessments. Each subject will receive oral TID doses of GSK2982772 in each treatment period. For TID dosing, GSK2982772 or placebo will be administered at 0 hr (the first dosing), 7 hr (the second dosing) and 14 hr (the third dosing) on Day 1 in each period. On Day 1, subjects will fast 8hr overnight prior to first dose. A breakfast will be served approximately 2hr after first dose. Lunch and dinner will be served between 2 to 3hr prior to second and third doses, respectively.
Washout Period	Will be at least 7 days between treatment period doses for an individual subject.
Follow-up	At least 7 days, and no greater than 14 days after last study treatment administration. If warranted, additional follow-up visits may be scheduled.

5.2. Number of Subjects

Sufficient Japanese healthy male subjects will be enrolled such that up to 12 subjects complete dosing and critical assessments.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence and start from the period to be replaced at the discretion of the GSK and in consultation with the principal investigator.

5.3. Sentinel Dosing

The doses will be staggered such that for each dose, on Day 1 of Period 1, 2 and 3, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety (AEs, clinical labs, vital signs, 12-Lead ECGs and findings during continuous cardiac telemetry) in the blind judgment of the principal investigator

and GSK Medical Monitor through at least 24 hrs after their third dose on Day 1, the remaining subjects may be randomized to dosing in that period.

5.4. Dose Escalation Decisions

The decision to proceed to the next dose level of GSK2982772 within the study will be made by principal investigator and GSK Medical Monitor per each dosing periods.

Dose escalation decisions will be based on blind data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: all AEs, clinical laboratory values, vital signs, 12-Lead ECG up to Day 4 (at discharge) and findings during continuous cardiac telemetry in the previous dose (Section 8.1.1.).

5.5. Participant and Study Completion

A participant is considered to have completed the study if he has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.6. Scientific Rationale for Study Design

This study will include a placebo control study, to allow for evaluation of AEs attributable to treatment versus those independent of treatment.

In Study 200975, 67 subjects were exposed to active treatment. GSK2982772 was well-tolerated, with no deaths or other non-fatal SAEs being reported. Sentinel dosing approach was taken in Study 200975, where two subjects receive placebo or GSK2982772 on Day 1 and the remaining subjects are dosed after safety evaluation at 24 hrs of preceding two subjects. Since this study is the first study in Japanese subjects, this study adopts a cautious approach including sentinel dosing and will include rigorous safety monitoring to confirm the safety profile prior to dose-escalation of single dose of the next dose strength, which was the same way taken in the past non-Japanese study.

In the 4 week repeat dose nonclinical toxicology studies, neurological related events (uncoordinated movement, irregular gait, trembling, hunched appearance and decreased activity) were observed in some rats and monkeys. On the other hand, in the 13 week repeat dose nonclinical toxicology studies in rats or monkeys, or in the 39 week repeat dose nonclinical toxicology study in monkeys, no neurological-related events were observed in rats or monkeys. There have been some reports of lethargy, abnormal dreams, and depressed mood in Study 200975 (See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_04]). This study includes neurological exams by considering these findings from Study 200975.

In the currently ongoing non-Japanese healthy volunteer study (Study 205184) being conducted in the United Kingdom (UK), several asymptomatic arthyhmias were detected in 6 out of 25 subjects treated with GSK2982772 or placebo. The study was temporarily

put on hold by GSK to assess the totality of these events. A formal review by the GSK Internal Cardiac Safety Panel, inclusive of both internal and external cardiologists, determined that the arrhythmic events were not likely related to GSK2982772 administration based on the timing and random occurrences of the events, the heterogeneity of the arrhythmias, the length of cardiac monitoring being performed during the study, and no findings in preclinical studies. Subsequently, the protocol was amended to increase the number of placebo subjects to balance randomization between active and placebo to understand the background cardiac patterns of subjects who are enrolled compared to when on treatment. Approval to proceed with the study was received from Medicines and Healthcare products Regulatory Agency (MHRA) on 22 March 2018. Study 200975 and Study 205184 did include telemetry, while the cardiac events related to the study drug were not observed in non-Japanese subkects including Study 205184, Since this study is the first study in Japanese subjects, telemetry will be planed in this study.

GSK2982772 concentrations decline rapidly until about 12 hrs post-dose, with a t1/2 of approximately 2 to 3 hrs. It, therefore, is considered sufficient to allow at least 7 days washout between dosing periods. Also, 7 days follow up after the last dose is considered to be sufficient for safety evaluation.

In the ongoing Study 205184, there are two TID dose regimens of 120 mg TID and 240 mg TID. This study plans also TID dose regimen, which allows to compare the PK between Japanese subjects and non-Japanese subjects in order to support dosing of GSK2982772 in Japanese patient population in the Phase 2b dose ranging studies.

5.7. Dose Justification

The initial starting dose planned is 60 mg TID and the maximum dose is 720 mg/day administered as 240 mg TID, which cover the dose range for the proposed Phase 2b study.

In Study 200975, all of the administered regimens (single dose; 0.1-120 mg, repeat dose; 20 and 60 mg QD, 60 and 120 mg BID for 14 days) appeared to be well tolerated, and no dose limiting AEs or safety findings were observed. There were no clinically significant patterns of abnormal vital sign measurements, physical and neurological examinations, 12-lead ECG and holter ECG changes or clinical laboratory (e.g., hematology, chemistry or urinalysis) findings observed in healthy subjects. There were no deaths or SAEs reported in the study.

Since the target dose per day currently planed in Phase IIb study is 720 mg, the dose regimens in Study 205184 in non-Japanese are 120 mg TID, 240 mg TID and 360 mg BID. For the 360 mg BID dose (single day dosing), one subject exceeded Cmax limit with several other subjects approaching the Cmax limit. In addtion, and the AUC(0-24) at 360 mg was also higher than that predicted but within the limits of stopping criteria. Based on the data in Study 205184, 240 mg TID is considered as the maximum dose in this study.

The predicted mean AUC(0-24) for the highest planned doses in the current study of 240 mg TID (40.2 μg･h/mL) approximates parity with the mean AUC(0-24) observed at the

NOAEL (30 mg/kg/day) in the 13 week repeat dose toxicity study in monkey (48.4 μg· h/mL) and is approximately 1/5th to 1/4th of the mean AUC(0-24) observed at the NOAEL (60 mg/kg/day) in the 39 week repeat dose toxicity study in monkey (182 ug· h/mL). Mean Cmax values for 240 mg TID (3.21 μg/mL) doses are predicted to be 1/4th of the mean Cmax observed at the NOAEL in the 13 week monkey study (12.3 μg/mL) and 1/7th of the mean Cmax at the NOAEL in the 39 week monkey study (23.2 μg/mL). Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_04].

The major circulating metabolite is an N-glucuronide which accounts for approximately 70% of drug related material in plasma. Since glucuronidation is a high capacity clearance mechanism it is unlikely that the kinetics of GSK2982772 will become saturable at the higher doses planned in this study.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 20 to 64 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Healthy as determined by the Investigators based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests, and ECG.

   A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigators in consultation with the GSK Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

   Note: Screened subjects with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigators

Weight

3. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5-24.9 kg/m^2 (inclusive).

Sex

4. Japanese Male

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and until follow up visit.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data
2. Abnormal blood pressure as determined by the investigators
3. Symptomatic herpes zoster within 3 months prior to screening
4. Evidence of active or latent TB as documented by medical history and examination, chest X-rays (anterior and lateral), and TB testing (T Spot. TB)
5. Alanine Aminotransferase (ALT) >1.5x upper limit of normal (ULN)
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
8. History of active infections within 14 days of first receiving study medication.
9. QTcF > 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

- For purposes of data analysis, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

10. History or diagnosis of obstructive sleep apnoea, or a significant respiratory disorder. Childhood asthma that was fully resolved is permitted.
11. History of active Suicidal Ideation Behaviour within the past 6 months or any history of attempted suicide in a participant's lifetime.
12. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.

Prior/Concomitant Therapy

13. Past or intended use of over-the-counter or prescription medication including herbal medications within 14 days prior to dosing.
14. Live vaccine(s) within 1 month prior to screening, or plans to receive such vaccines during the study

Prior/Concurrent Clinical Study Experience

15. History of donation of blood or blood products ≥ 400 mL within 3 months or ≥ 200 mL within 1 month prior to screening
16. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
17. The subject has participated in a other clinical study or other medical research within 4 months prior to the first dosing day in the current study.

Diagnostic assessments

18. The subject is positive Serological test for syphilis (RPR and TP), Tuberculosis, HIV Antigen/Antibody, Hep B surface antigen (HbsAg), Hep C virus (HCV) antibody, or HTLV-1 antibody at screening.
19. Positive pre-study drug screen
20. Regular use of known drugs of abuse

Other Exclusions

21. Regular alcohol consumption within 6 months prior to the study defined as:
    - For an average weekly intake of > 14 units for males. One unit is equivalent to 350 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits
22. Smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening
23. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigators or GSK Medical Monitor, contraindicates participation in the study

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the start of study treatment until follow-up visit.

Once in the clinical unit subjects will not be allowed to eat anything other than the food provided by the study centre.

- Subjects must then fast from all food and drink (except water) for 8 hrs prior to first dose.
- Subjects must then fast from all food and drink (except water) for 8 hrs prior to any clinical laboratory evaluations.
- Water is permitted with dosing and at all times except 1 hr pre-dose through 2 hrs post-dose.
- On Day 1, breakfast will be served approximately 2 hr after first dose. Lunch will be served between 2 to 3 hr prior to second dose. Dinner will be served between 2 to 3 hr prior to third dose. On Day 2-3, meal will be served per unit schedule. Mealtime will be described in SRM.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing period, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hrs before the start of dosing until after collection of the final PK sample.
- During each dosing period, subjects will abstain from alcohol for 24 hrs before the start of dosing until after collection of the final PK sample.
- Use of tobacco, nicotine, or nicotine-containing products (including nicotine patch) will not be allowed from 6-months before screening until after collection of the final PK sample.

6.3.3. Activity

Subjects will abstain from strenuous exercise for 48 hrs prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watching television, read).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure judged ineligible) may not be rescreened.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name	**GSK2982772 30 mg**	**GSK2982772 120 mg**	**Placebo to match GSK2982772 30mg**	**Placebo to match GSK2982772 120mg**
Dosage formulation	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s)	30 mg	120 mg	NA	NA
Route of Administration	Oral	Oral	Oral	Oral
Dosing instructions	As directed	As directed	As directed	As directed
Physical description	White to almost white, round, film-coated tablet	White to almost white, oval, film-coated tablet	White to almost white, round, film-coated tablet	White to almost white, oval, film-coated tablet
Packaging and Labelling	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.
Manufacturer	Aptuit (Italy)	GSK (UK)	Aptuit (Italy)	GSK (UK)

7.2. Method of Treatment Assignment

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 4 groups, according to the randomization schedule generated prior to the study by the Biomedical Data Sciences Department at GSK. Each participant will be dispensed blinded study treatment, labelled with his unique randomization number, throughout the study.

Subjects will be randomized to one of four sequences (A, B, C and D), where the treatments in the sequences are:

- A: Placebo TID / 60 mg TID / 120 mg TID / 240 mg TID
- B: 60 mg TID / Placebo TID / 120 mg TID / 240 mg TID
- C: 60 mg TID / 120 mg TID / Placebo TID / 240 mg TID
- D: 60 mg TID / 120 mg TID / 240 mg TID / Placebo TID

7.3. Blinding

This study will be a double-blind with respect to subjects, investigators and site staff (with the exception of the unblinded site pharmacist).

Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study.

A participant will be withdrawn if the participant's treatment code is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the case report form (CRF).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to principal investigator in accordance with local regulations and/or GSK policy.

7.4. Preparation/Handling/Storage/Accountability

1. The investigators or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants randomized 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 labeled storage conditions with access limited to the investigators and authorized site staff.
3. The investigators, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
    - Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigators, where this is required by local laws, or is available upon request from GSK.

7.5. Treatment Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study treatment directly from the investigators or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The GSK Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigators and GSK, the medication will not interfere with the study.

7.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK, or with GSK2982772, after completion of the study because only healthy subjects are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Dose Stopping Criteria

The decision to proceed to the next dose level of GSK2982772 in each part of this study will be made by the principal investigator and GSK Medical Monitor based on safety results (AEs, clinical labs, vital signs, 12-Lead ECGs and findings during continuous cardiac telemetry) obtained in at least 6 subjects having received active treatment (GSK2982772) at the prior dose level.

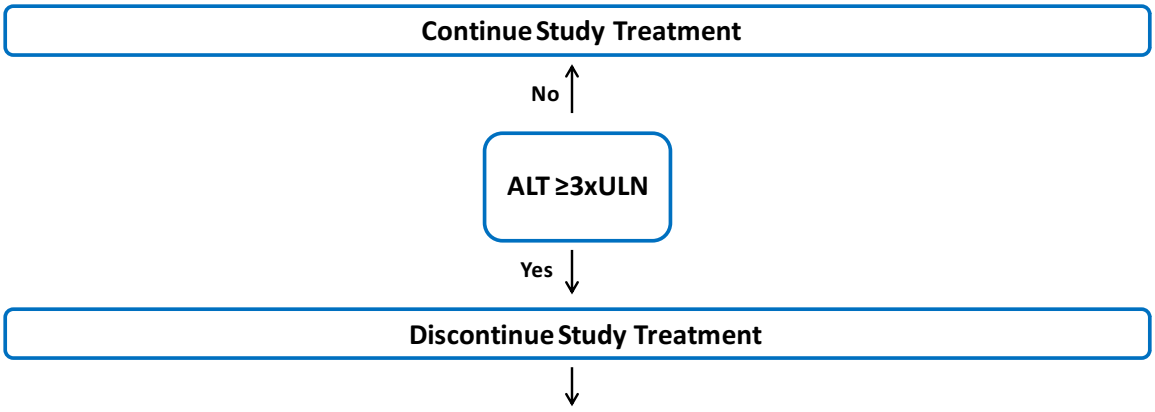
The principal investigator and the GSK Medical Monitor will review the following and dosing will be halted and progression to the next higher dose level stopped if:

- One (1) or more subjects experience a SAE which has a reasonable possibility of relation to study treatment.
- Two (2) or more subjects experience a severe or clinically significant non-serious AE (based upon principal investigator judgment) which has a reasonable possibility of relation to study treatment.
- Two (2) or more subjects experience the same AE of moderate severity which has a reasonable possibility of relation to study treatment.
- Consistent Common Terminology Criteria for Adverse Events (CTCAE) Nervous System AEs of any grade occur across subjects that have a reasonable possibility of relation to study treatment.
- Female partner become pregnant during the treatment period.

8.1.2. Liver Chemistry Stopping Criteria

Study treatment will be discontinued for a participant if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.3. QTc Stopping Criteria

A subject that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.
See Section 9.3.4. about 12-lead ECG.

- QTcF > 500 msec
- QTcF increase > 60 msec from baseline

8.1.4. Individual Safety Stopping Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the principal investigator, after consultation with the GSK Medical Monitor, is possibly, probably or definitely related to investigational product.
- The participant develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria (See Section 8.1.2) or QTc stopping criteria (see Section 8.1.3) are met.

8.1.5. Nervous System Stopping Criteria

The CTCAE Nervous System disorder is a monitoring tool which provides the investigators the appropriate guidance for grading of a neurological event. The significance of any neurological event experienced by a subject will be determined based on clinical judgment, characteristics of the event and/or based upon changes from a baseline assessment.

The principal investigator and the GSK Medical Monitor will review all neurological events utilizing the CTCAE Nervous System disorder criteria and dosing may be halted if and progression to the next higher dose level stopped as per Section 8.1.1.

A subject will be withdrawn from the study if:

- A Grade 3 or greater CTCAE Nervous System disorder finding is observed or a significant neurologic change from a subject's baseline physical examination is observed.
- Any adverse event included in the CTCAE for Nervous System disorder, which is also considered to be clinically significant by the principal investigator, will be reviewed for potential subject withdrawal.

Note: Appendix 9 (Section 8.1.1) provides Guidance for Grading AEs that is taken from the CTCAE Version 4.03.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigators for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the GSK may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigators or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the GSK immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The principal investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 400 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigators and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

9.1.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the GSK or designee immediately and under no circumstance should this exceed 24 hrs, as indicated in Appendix 4. The

investigators will submit any updated SAE data to the GSK within 24 hrs of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigators learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigators must promptly notify the GSK.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigators is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non serious AEs of special interest (as defined in Section 3.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.1.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigators to the GSK of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- GSK has a legal responsibility to notify both the local regulatory authority about the safety of a study treatment under clinical investigation. The GSK will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to principal investigator as necessary.
- An principal investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the GSK will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the follow-up visit.

- If a pregnancy is reported, the investigators should inform GSK within 24 hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

For this study, any dose of GSK2982772 greater than 720 mg within a 24-hr time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigators should:

1. Contact the GSK Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days for GSK2982772).
3. Obtain a plasma sample for PK analysis if requested by the GSK Medical Monitor (determined on a case-by-case basis).
4. 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 investigators in consultation with the GSK Medical Monitor based on the clinical evaluation of the participant.

9.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will only be measured and recorded on screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.2. Neurological Examinations

Neurological examination will include, at a minimum, assessment of: mental status, gait, balance, coordination, cranial nerves, motor power, reflexes, and sensory system (light touch and pain). Assessments will be standardized across all scheduled time points (see SoA). Significant changes from the baseline or any clinically significant changes will be noted as part of further scheduled examinations or unscheduled examinations (if needed).

Clinically significant abnormalities or changes in status from baseline will be:

- entered as an adverse event,
- may trigger increased monitoring of the subject(s),
- may result in withdrawal of the subject (see Section 8.2),
- may result in referral to a specialist.

9.3.3. Vital Signs

- Axillary temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

9.3.4. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.3 for QTc withdrawal criteria and additional QTcF readings that may be necessary.
- Single ECGs will be obtained at each time point.
- If QTcF is appeared the value applied the discontinuation criteria, ECG must be conducted two additional readings and be confirmed whether apply the discontinuation criteria.
- Continuous cardiac telemetry will be performed at time points indicated in the SoA (see Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the subject’s source documents.

9.3.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigators must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigators to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigators or GSK Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigators, the etiology should be identified and the GSK notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual of study site and the SoA.

9.3.6. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There is some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some subjects. Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Participants being treated with GSK2982772 should be monitored appropriately and observed closely for SIB or any other unusual changes in behaviour. All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

Families of participants being treated with GSK2982772 should be alerted about the need to monitor participants for the emergence of unusual changes in behaviour, as well as the emergence of SIB and to report such symptoms immediately to the study investigators.

9.4. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2982772 as specified in the SoA. Instructions for the collection and handling of biological samples will be described in the SRM. The actual date and time (24-hr clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK2982772. Samples collected for analyses of GSK2982772 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.5. Genetics

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese ethical guidelines for human genome/gene analysis research.

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

10. STATISTICAL CONSIDERATIONS

The objectives of this study are to evaluate safety, tolerability and PK of GSK2982772 in healthy Japanese subjects. No formal statistical hypotheses will be tested. Descriptive statistics will be used to assess safety and tolerability. An estimation approach will be used to address the pharmacokinetic study objectives, where point estimates and corresponding confidence intervals (CI) will be constructed.

10.1. Sample Size Determination

In a 4-way crossover design, total 12 subjects will be randomized in four groups with a randomization ratio of 1:1:1:1; 3 subjects in each group. The sample size for this study is based on the feasibility rather than statistical considerations. The number of subjects who will take a placebo, 60 mg, 120 mg, or 240 mg dose will be 12 with totalizing four groups. No calculations for formal power and sample size are performed.

One of the objectives of this study is safety, where a number of safety events are of interest. A maximum of 12 subjects will receive each active dose and; therefore, if 0/12 of a particular safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 26.5% could not be ruled out. Whereas if 1/12 of the same safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 38.5% could not be ruled out.

Using a Bayesian approach to determine the CI around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 12 then the posterior distribution would be Beta (2, 12), as outlined in Figure 1. Thus, we can 95% certain that the true probability of the safety event lies between 0.02 and 0.36.

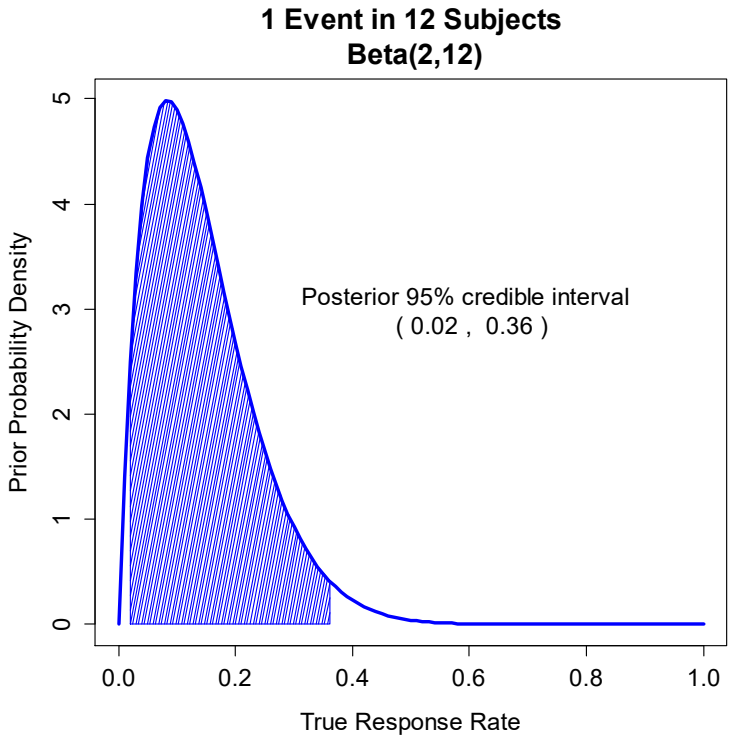


Figure 1 Bayesian Approach to Determine Confidence in Safety Event

Between-subject variability of Cmax and AUC(0-t) of GSK2982772 is estimated to be 32.9% (CV%) and 23.5% (CV%), respectively (based on PK results of 60 mg BID on Day 1 and 120 mg BID on Day1 from Study 200975 Part B). Based on these variability estimates and the sample size of 12, the upper limit value of 95% CI of geometric mean of Cmax and AUC(0-t) is estimated to be approximately 22.6% and 15.9%, respectively.

10.2. Sample Size Sensitivity

Different safety event rates were investigated for sample size sensitivity analysis. If the number of subjects who completed each active dose was different, then the true incidence rates of safety events that could not be ruled out would change. These changes are outlined as below.

Completed N	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
12	2	48.4%
	3	57.2%
	4	65.1%
11	0	28.5%
	1	41.3%
	2	51.8%
	3	61.0%
10	0	30.8%
	1	44.5%
	2	55.6%
	3	65.2%

Following table shows how the results could have variabilities with changing between-subject estimates of variability (CV%) and number of subjects. Estimates of the upper limit values of 95% CI of geometric mean are described using proportions (%) of variability to geometric mean of PK parameters.

N	Estimate of between-subject variability (CV%)			
	20	30	40	50
11	14.2%	21.8%	29.5%	37.3%
12	13.4%	20.5%	27.7%	35.0%
13	12.7%	19.4%	26.2%	33.0%
14	12.1%	18.4%	24.9%	31.4%

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All subjects who have a screening visit will be included.
Enrolled	All subjects who passed screening and entered the study will be included. Note screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.

Population	Description
Safety analyses	All subjects who have received at least one dose of study treatment will be included. This population will be used for the safety analyses.
PK analyses	All subjects in the Safety population for whom a PK sample has been obtained and analyzed will be included. This population will be used for the PK analyses.

10.4. Statistical Analyses

10.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

The tables, figures, and listings will use the Safety Population unless otherwise specified. AEs, changes in clinical laboratory values, 12-Lead ECGs, findings during continuous cardiac telemetry and vital signs will be summarized by dose group (i.e. placebo, 60 mg, 120 mg, and 240 mg) to assess the safety and tolerability of GSK2982772. The safety and tolerability results will not to be formally compared between each group and comparison with placebo will be based on review of descriptive summaries.

10.4.2. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population.

Statistical Analysis Methods

Plasma GSK2982772 concentration-time data will be analysed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following PK parameters will be determined, as data permit: AUC(0-24), AUC(0-7), AUC(7-14) and AUC(14-24), Cmax following each dose, time to maximum observed plasma drug concentration (Tmax) following each dose,t1/2 following the third dose, observed trough plasma concentrations (C0, C7, C14 and C24).

PK data will be presented in graphical and/or tabular form and will be summarised descriptively.

Listings will be generated and summary statistics (n, arithmetic mean with associated 95% CI, standard deviation (SD), minimum, median, maximum, geometric mean with associated 95% CI, SD on log-scale and %CVb) will be calculated for each derived plasma PK parameter for each dose.

The PK-dose relationship will be examined graphically by plotting derived plasma PK parameters for each dose group. Dose proportionality for AUC(0-24), AUC(0-7) and Cmax following the first dose will be assessed by using a power model as described below:

$\log_e$ (PK parameter) = $\mu + S_i + \beta * \log_e (D_j) + \varepsilon_{ij}$

where μ is the intercept, β is the slope, S_i is the random effect for subject i, D_j is the dose (j = 60 mg, 120 mg, or 240 mg), ε_{ij} is the random error. Point estimates for the slope of PK parameters and their associated 90% CI will be presented.

10.4.3. Interim Analyses

A review of safety data will be conducted at the end of each period.

The decision to proceed to higher dose strengths will be made by principal investigator and GSK's Medical Monitor based on assessment of safety and tolerability at the preceding dose. This review can include individual subject data.

11. REFERENCES

GSK2982772 Investigator's Brochure, GlaxoSmithKline Document Number 2014N204126_04.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADL	Activities of daily life
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
AUC	Area under concentration-time curve
AUC(0-7)	Area under the concentration-time curve from time 0 to 7 hr
AUC(7-14)	Area under the concentration-time curve from time 7 to 14 hr
AUC(14-24)	Area under the concentration-time curve from time 14 to 24 hr
AUC(0-t)	Area under the concentration-time curve from time 0 to the time of the last measurable drug concentration
AUC(0-∞)	Area under the concentration-time curve from time 0 to infinity
BID	Bis in die
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulation
CI	Confidence interval
Cmax	Maximum observed plasma drug concentration
C0	Plasma drug concetration at pre-dose
C7	Plasma drug concetration at 7 hr after dosing
C14	Plasma drug concetration at 14 hr after dosing
C24	Plasma drug concetration at 24 hr after dosing
CNS	Central nervous system
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTN	Clinical Trial Notification
CV	Coefficient of variance
CYP	Cytochrome P450
DAMP	Damage associated molecular pattern
e.g.	Exempli gratia
ECG	Electrocardiogram
FLAIR	FLuid-Attenuated Inversion Recovery
FTiH	First Time in Human
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h/hr(s)	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
Hep B	Hepatitis B

Hep C	Hepatitis C
HIV	Human immunodeficiency virus
HTLV-1	Human T-cell leulemia virus type 1
i.e.	id est
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
kg	Kilogram
loge	Natural logarithm
µg	Micrograms
mg	Milligrams
min	Minute
mL	Milliliter
msec	Milliseconds
MV	Minute volume
MTX	Methotrexate
m^2	Square metre
NA	Not applicable
ng	Nanograms
nL	Nanoliter
NOS	Not otherwise specified
NOAEL	No Observable Adverse Effect Level
OAT3	Organic anion transporter 3
P-gp	P-glycoprotein
pH	Pondus Hydrogenii
PK	Pharmacokinetics
PsO	Psoriasis
PR	Pulse rate
QD	Quaque die
RA	Rheumatoid arthritis
RIP1	Receptor-interacting serine/threonine protein-1
RNA	Ribonucleic acid
RPR	Rapid Plasma Reagin
SAE	Serious adverse event
SAS	Subarachnoid space
SD	Standard deviation
Ser	Serine
SIB	Suicidal Ideation and Behaviour
SoA	Schedule of Activities
SRM	Study Reference Manual

$t_{1/2}$	Terminal half-life
TB	Tuberculosis
Thr	Threonine
TID	Ter in die
T_{max}	Time to maximum observed drug concentration
TNF(α)	Tumour necrosis factor (α)
TNFR1	Tumour necrosis factor receptor-1
TP	Treponema pallidum
UC	Ulcerative colitis
ULN	Upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH ‰Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Uric acid	TG	Total Cholesterol	LDL-cholesterol
	HDL-cholesterol	LDH	GGT	CK (CPK)
	Amylase	Chloride	Phosphorus	CRP
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine drug screen (to include at minimum: Phencyclidines [PCP], Benzodiazepines [BZO], Cocaine [COC], Amphetamines [AMP], Tetrahydrocannabinol [THC], Opiates [OPI], Barbiturates [BAR], Trycyclic antidepressants [TCA]) • Serology (Syphilis [RPR & TP], TB, HIV antigen/antibody, HTLV-1 antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (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).

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the GSK with sufficient, accurate financial information as requested to allow the GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who received rescreening must be re-consented the ICF(s).
- The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the GSK. Any participant records or datasets that are transferred to the GSK will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the GSK, by appropriate IRB members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the GSK before submission. This allows the GSK to protect proprietary information and to provide comments.

- The GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the GSK will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- 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.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the GSK or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The GSK or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional

policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the GSK. No records may be transferred to another location or party without written notification to the GSK.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the list of the source documents.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the GSK or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the GSK's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.
- 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 study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- 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 before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- 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 participant'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 participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity • 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 with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include 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.

Recording AE and SAE

AE 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) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 24 hrs of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hrs. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hrs of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form. • Contacts for SAE reporting can be found in Appendix 8.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **GSK Medical Monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Appendix 8.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use method of contraception with a failure rate of < 1% per year as described in Table 2 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- In addition male participants must refrain from donating sperm for duration of study and until follow up visit

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the Women of Childbearing Potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the*

preferred and usual lifestyle of the participant.)

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and until follow up visit.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will discontinue study treatment and attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hrs 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.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2982772 or immuno-inflammatory and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2982772 or study treatments of this drug class, and immuno-inflammatory diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed for UDP-glucuronosyltransferase 1-9 family, polypeptide A cluster enzyme that is encoded by the UGT1A9 gene complex. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2982772 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- Samples will be given a code and stored securely.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2982772 (or study treatments of this class) continues but no longer than 15 years after the last subject last visit or other period as per local requirements.
- If particinpant chooses to stop the pharmacogenetics part of the study after giving a sample, GSK will not conduct any new tests on the sample. GSK will destroy the sample. GSK will keep and use any results generated before you stopped participating in the pharmacogenetics study.
- GSK will only use the coded results to verify or show the quality of analyses that have already been reported. GSK will take steps to ensure that your coded results are not used in any new analyses. If new analyses are conducted then GSK will make sure that the subject's number will be deleted.
- GSK may provide your genetic information generated from your sample for research with other companies or universities to learn more about other medicines, this immuno-inflammatory disease and other disease, only by deleting the subject number before it is provided, so that provided information will not be identified in any way and your privacy is protected.

- If GSK decides to use your sample and/or your genetic information for a different study, GSK will ask participant for his permission again or GSK will ask an adequate committee to review the study from ethical standpoint.

12.7. Appendix 7: Liver Safety Required Actions and Follow up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 3xULN

If ALT ≥ 3xULN AND bilirubin[1,2] ≥ 2xULN (> 35% direct bilirubin) or INR > 1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hrs
• 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, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR > 1.5
• 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, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT ≥ 3xULN AND bilirubin < 2xULN and INR ≤ 1.5:</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain plasma sample for pharmacokinetic (PK) analysis, obtained within 24 hrs of last dose[4]
• 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

If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR > 1.5:</td></tr>
</table>

Liver Chemistry Stopping 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	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • 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. Includes: Hepatitis A immunoglobulin M (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)
4. 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 PK 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.

12.8. Appendix 8: Country-specific requirements

12.8.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (Ministry of Health and Welfare (MHW) Notification No.28 dated 27th March, 1997)" and the Pharmaceuticals and Medical Devices Act.

GSK will submit the Clinical Trial Notification (CTN) to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

12.8.2. Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential participant of the study including the written information. The investigator (or subinvestigator) should provide the participant ample time and opportunity to inquire about details of the study. The participant should sign and personally date the consent form. The participant may consider the content of the written information at home. The person, who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the participant.

12.8.3. Study Period

JUL 2018 - SEP 2018

12.8.4. Study Administrative Structure

Sponsor Legal Registered Address:

GlaxoSmithKline K.K. (GSK)
Akasaka Intercity AIR, 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
Study Director: PPD Head, Medicines Development, Clinical Pharmacology & Science Promotion Office

Sponsor Contact Address:

Lead Author:
PPD Manager, Medicines Development, Clinical Pharmacology & Science Promotion Office

Sponsor's Emergency Contact Information (10:00-18:00, Monday to Friday, except national holidays and year-end and new-year holidays);

Medicines Development (Clinical Pharmacology), GlaxoSmithKline K.K.
TEL: PPD (direct dialling)
FAX: PPD

Contact Information at Night and on Holidays (Monday to Friday: 18:00-10:00, Saturday, Sunday, national holidays, year-end and new-year holidays)
PPD (mobile: PPD

GSK Medical Monitor / Contact Address for SAE

PPD
GlaxoSmithKline K.K. (GSK)
Akasaka Intercity AIR, 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
TEL: PPD (mobile)／PPD (direct dialling)
FAX: PPD

Medical Institution and Investigator

PPD
SOUSEIKAI Hakata Clinic
6-18 Tenyamatchi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

Laboratories

Clinical Laboratory (except HTLV-1 serology and TB)
SOUSEIKAI Hakata Clinic
Person in charge: PPD
6-18 Tenyamachi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

HTLV-1 serology and TB (If subject meet Liver chemistry stopping criteria, include anti-nuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins, and viral hepatitis serology described in Appendix 7, but except HBsAg)
Person in charge: PPD
LSI Medience Inc.
30-1 Shimura 3-chome, Itabashi-ku, Tokyo 174-8555, Japan
TEL: PPD
FAX: PPD

Pharmacokinetics Measurement Facilities
Covance Laboratories Limited
Person in charge: PPD
Otley Road, Harrogate, North Yorkshire, HG3 1PY, UK
TEL: PPD

Gx Research Administration (Sample Management , Sample Storage Facility, DNA Extraction Facility)
Contact person: PPD
Q2 Solutions
Q Squared Solutions (Quest) LLC
27027 Tourney Road, Suite 2E
Valencia, CA 91355
USA
TEL: PPD
FAX: PPD

Contract research organization

Role: Study Monitoring
Person in charge (Monitor Leader): PPD
Mediscience Planning Inc.
2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Protocol & Informed Consent Form)
Person in charge: PPD
Mediscience Planning Inc.
2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Clinical Study Report)
Person in charge: PPD
Mediscience Planning Inc.
2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Pharmacokineic Parameter Derivation
Person in charge: PPD
Mediscience Planning Inc.
1-2-1 Nihonbashi hamacho, Chuo-ku, Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

Role: Data Loading
Person in charge: PPD
Mediscience Planning Inc.
1-2-1 Nihonbashi hamacho, Chuo-ku, Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

12.9. Appendix 9: Nervous System Adverse Events (CTCAE Criteria)

Taken from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

The purpose of this Appendix is to provide guidance and is to be used in conjunction with the Investigator's judgment.

Table 3 Guidance For Grading Adverse Events

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental Activities of daily life (ADL)	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-	A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-	A disorder characterized by systematic and extensive loss of memory.
Aphonia	-	-	Voicelessness; unable to speak	-	-	A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-	A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-	A disorder characterized by a conspicuous change in cognitive function.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-	A disorder characterized by a deterioration in the ability to concentrate.
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death	A disorder characterized by a decrease in ability to perceive and respond.
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-	A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-	A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-	A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-	A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention		A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
				indicated		
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a pathologic process involving the brain.
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by a reduction in the strength of the facial muscles.
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the facial nerve (seventh cranial nerve).
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention	Death	A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
	indicated			indicated		
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-	A disorder characterized by characterized by excessive sleepiness during the daytime.
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, Intracranial Pressure (ICP) monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by bleeding from the cranium.
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-	A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum ± mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum ± moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death	A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-	A disorder characterized by a deterioration in memory function.
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by uncontrolled and purposeless movements.
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by intense painful sensation along a nerve or

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
						group of nerves.
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involuntary movements of the eyeballs.
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the olfactory nerve (first cranial nerve).
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral motor nerves.
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.
Presyncope	-	Present (e.g., near fainting)	-	-	-	A disorder characterized by an episode of lightheadedness and

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
						dizziness which may precede an episode of syncope.
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by paralysis of the recurrent laryngeal nerve.
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by characterized by excessive sleepiness and drowsiness.
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death	A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.
Syncope	-	-	Fainting; orthostatic collapse	-	-	A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-	A disorder characterized by a brief attack (less than 24 hrs) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	-

12.10. Appendix 10: Protocol Amendment History

Not applicable