NOVARTIS

Clinical Development

FGF401

Protocol CFGF401X2101 / NCT02325739

A phase I/II, multicenter, open-label study of oral FGF401 in adult patients with hepatocellular carcinoma or solid malignancies characterized by positive FGFR4 and KLB expression

Document type	Amended Protocol Version
EUDRACT number	2014-002929-35
Version number	05 (Clean)
Development phase	I
Document status	Final
Release date	27-Sep-2018

[redacted]

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomic-Therapeutic-Chemical classification
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
b.i.d.	*bis in diem*/twice a day
BAS	Bile acid sequestrant
BCLC	Barcelona Clinic Liver Cancer
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics classification system
BHLRM	Bayesian hierarchical logistic regression model
BLRM	Bayesian logistic regression model
BOR	Best overall response
BSA	Body surface area
BSEP	Bile Salt Export Pump
BUN	Blood urea nitrogen
cfDNA	Cell free DNA
CL	Clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical study report
CRS	Cytokine Release Syndrome
CTCAE	Common terminology criteria for adverse events
C_{trough}	The concentration that is just prior to the beginning of, or at the end, of a dosing interval
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-Drug interaction
DDS	Dose-determining analysis set
DLT	Dose Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
EWOC	Escalation with overdose control
FAS	full analysis set
FGF	Fibroblast growth factor

[redacted]

FGFR	Fibroblast growth factor receptor
FU	follow-up
G-CSF	Granulocyte colony stimulating factor
GI	Gastro-Intestinal
GLP	Good laboratory practice
GM-CSF	Granulocyte macrophage colony stimulating factor
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HLM	Human liver microsomes
i.v.	intravenous
IC_{50}	Inhibitory concentration (at half-maximum inhibition)
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IG	Immunogenicity
IL	Interleukin
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
IUD	intrauterine device
IUS	intrauterine system
KD	constant of dissociation
KLB	β-Klotho
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
M-CSF	Macrophage colony stimulating factor
MRP	Multidrug resistance-associated protein
MTD	Maximum Tolerated Dose
NADPH	Nicotinamide adenine dinucleotide phosphate
NTCP	Na^+-taurocholate cotransporting polypeptide
OATP	Organic anion-transporting polypeptide
ORR	Overall response rate
OS	Overall survival
p.o.	*per os*/by mouth/orally
P-gp	P-glycoprotein
p/t	Phosphorylated over total
PAS	Pharmacokinetic analysis set
PBMCs	Peripheral blood mononuclear cells
PBPK	Physiologically-based pharmacokinetics
PD	Pharmacodynamics

[redacted]

PD-1	Programmed Death-1
PD-L	Programmed Death-Ligand
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PPI	Proton pump inhibitors
PPS	Per-Protocol Set
PT	Prothrombin time
Q3W	Every three weeks
Raf	Rapidly accelerated fibrosarcoma
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SD	Stable Disease
SEB	Staphylococcal Enterotoxin B
SI unit	International System of Units
SJS	Stevens Johnson Syndrome
SOP	Standard Operating Procedure
$T_{1/2}$	Terminal half-life
TACE	Transarterial chemoembolization
TEN	Lyell syndrome/toxic epidermal necrolysis
T_{max}	Time to reach observed maximum concentration
TNFα	Tumor necrosis factor-α
TSH	Thyroid-stimulating hormone
TTP	Time to progression
UGT	Uridine diphosphate glucuronyltransferase
ULN	Upper limit of normal
Vss	Volume of distribution (at steady state)

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q21 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Stratum	A group of patients enrolled and treated in same specific condition (e.g. food intake condition)
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject who enrolls in the study
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

[redacted]

Protocol summary:

Protocol number	CFGF401X2101
Title	A phase I/II, multicenter, open-label study of oral FGF401 in adult patients with hepatocellular carcinoma or other solid tumors characterized by positive FGFR4 and KLB expression
Brief title	FGF401 in HCC and solid tumors characterized by positive FGFR4 and KLB expression
Sponsor and Clinical Phase	Novartis Phase I/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of FGF401 as single agent and in combination with PDR001 in patients with hepatocellular carcinoma and as single agent in other solid tumors characterized by positive FGFR4 and KLB expression; and to estimate the preliminary anti-tumor activity of FGF401 single agent and in combination with PDR001 in these populations. Based on preclinical studies, FGF401 is a highly potent, selective FGFR4 inhibitor, thereby making it a good candidate for use in the clinic. Positive prediction for sensitivity to FGF401 was identified to be associated with positive expression of FGFR4, KLB and FGF19. Based on the emerging clinical efficacy results, the combination of FGF401 with PDR001 will be evaluated in parallel to the FGF401 single agent, in unselected HCC population for both parts of the study.
Primary Objective(s) and Key Secondary Objective	Phase I: To estimate the MTD or RP2D of FGF401 single agent and in combination with PDR001 Phase II: To investigate the anti-tumor activity of FGF401 single agent and in combination with PDR001
Secondary Objectives	● To characterize the safety and tolerability of FGF401 single agent and in combination with PDR001 ● To further investigate the anti-tumor activity of FGF401 single agent and in combination with PDR001 ● To characterize the PK properties of FGF401 single agent and in combination with PDR001 ● To evaluate food effect on FGF401 exposure and safety profile
Study design	This study has been designed as a phase I/II, multi-center, open-label study starting with a phase I dose escalation part followed by a phase II dose expansion part. Oral FGF401 and intravenous PDR001 (for the FGF401 and PDR001 combination part) will be administered as per protocol until patient experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent. A cycle is defined as 21 days. The phase II part of the FGF401 and PDR001 combination has a 2-stage study design with an interim efficacy analysis in unselected HCC patients and a sub-group futility analysis, based on FGF19 pathway activation if the efficacy criteria are not satisfied. Enrollment with a molecularly selected population will continue at Stage 2 if the futility criteria are not satisfied.
Population	Phase I-FGF401 single agent: adult patients with hepatocellular carcinoma or other solid malignancies characterized by positive FGFR4 and KLB expression. Phase II-FGF401 single agent: Group 1: adult HCC patients from Asian countries Group 2: adult HCC patients from non-Asian regions Group 3: adult other solid tumor patients, characterized by positive FGFR4 and KLB expression regardless of geography FGF401 and PDR001 combination: adult patients with advanced HCC

[redacted]

Key Inclusion criteria	1. Patients (male or female) ≥ 18 years of age 2. ECOG Performance Status ≤ 1 3. Presence of at least one measurable lesion according to RECIST v1.1. 4. FGF401 single agent-Phase I and Phase II-Group 3: Patients with confirmed positive expression of FGFR4 and KLB at pre-screening. 5. For HCC patients: the diagnosis must be made based on AASLD Guidelines with confirmed stage C advanced HCC (BCLC staging classification). Current cirrhotic status of Child-Pugh class A (5-6 points), with no encephalopathy and/or ascites. 6. FGF401 single agent-Phase I and Phase II, Group 3: Patients with HCC or advanced solid tumors, who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists. 7. FGF401 single agent-Phase II, Groups 1 and 2: HCC patients previously treated with sorafenib for advanced HCC with documented disease progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment. 8. FGF401 in combination with PDR001-Phase I and Phase II: Advanced HCC patients who have received up to 2 previous lines of systemic treatment and one treatment must have included sorafenib with documented disease progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment 9. FGF401 in combination with PDR001-Phase II-Stage 2: Documented FGF19 expression level and/or FGF19 pathway activation
Key Exclusion criteria	1. Previous treatment with a selective FGF19-FGFR4 targeted therapy and/or pan-FGFR inhibitor. 2. For HCC patients in FGF401 single agent-Phase II part: any previous systemic anti-cancer therapies other than sorafenib or any anti-cancer therapy (including locoregional therapy) after disease progression during or after sorafenib treatment. 3. Ongoing active diarrhea requiring medications (e.g. BAS, loperamide) 4. Irritable bowel syndrome with signs/symptoms and requires medications 5. Symptomatic CNS metastases which are neurologically unstable or requiring increasing doses of steroids to control their CNS disease. 6. Patient having out of range laboratory values defined as: ● Hematology Hemoglobin ≤ 9 g/dL (SI Units: 90 g/L) Platelet count < 75000/mm3 Absolute neutrophil count (ANC) < 1500/mm3 ● Chemistry Total bilirubin > 1.5 x ULN AST and/or ALT > 3 x ULN Serum creatinine > 1.5 x ULN and/or creatinine clearance < 40 mL/min ● Coagulation: PT > 4 seconds more than the ULN or INR > 1.7 7. Unable to stop any prohibited medications, including CYP1A2, CYP2C9 and CYP3A4/5 substrates with a narrow therapeutic index and known BSEP efflux transporter inhibitors. Additional exclusion criteria for FGF401 and PDR001 combination: 8. Impaired cardiac function 9. History of liver or other organ transplantation 10. Patients who discontinued prior anti-PD-1/PD-L1 therapy due to an anti PD-1/PD-L1-related toxicity
Investigational and reference therapy	The investigational therapy is FGF401 single agent and FGF401 in combination with PDR001. There is no reference therapy.
Efficacy assessments	Tumor assessment per RECIST v1.1 for FGF401 single agent; RECIST v1.1 and irRC for FGF401+PDR001 combination
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs

[redacted]

Other assessments	PK parameters Immunogenicity analysis for PDR001 [redacted]
Data analysis	Phase I: in order to estimate the MTD and/or RP2D of the FGF401 single agent and in combination with PDR001, the corresponding primary analysis methods are based on Bayesian adaptive models for the dose escalation with overdose control (EWOC) principle. Phase II: For the FGF401 single agent, anti-tumor activity will be primarily assessed in terms of overall response rate (ORR) for solid tumor patients and time to progression (TTP) for HCC patients. For FGF401 in combination with PDR001, anti-tumor activity will be primarily assessed in terms of ORR for HCC patients. The study data will be analyzed and reported based on all patients' data of the Phase I and Phase II parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study.
Key words	Phase I/II, FGF401, PDR001, PD-1, FGFR4 selective inhibitor, positive expression of FGFR4, KLB, FGF19 pathway

[redacted]

Amendment 5 (27-Sep-2018)

Amendment rationale

The main purposes of this amendment are:

- To incorporate health authority-requested language requiring study treatment discontinuation in the event of Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) (already implemented as part of an urgent safety measure released on 15 June 2018) and,
- To reduce study visits and assessments to ease the burden on patients who have been on study for more than 7 cycles, while maintaining access to study treatment and monitoring safety.

After the occurrence of a case of Stevens-Johnson syndrome in a study with PDR001 in combination with another investigational agent, the dose modification guidelines for protocols using PDR001 were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/toxic epidermal necrolysis (TEN). This change has already been implemented as part of an urgent safety measure released on 15 June 2018. This protocol amendment is now finalizing these changes in the dose modification section and corresponding tables describing the criteria for interruption and re-initiation of study treatment.

The primary objectives in the Phase I parts (FGF401 single agent and in combination with PDR001) of the study have been reached. Enrollment in the Phase II part of the FGF401 single agent has been completed. As of 03 July 2018, patient enrollment in this study has been halted and the phase II part of the FGF401 in combination with PDR001 will not be initiated. This enrollment halt was due to business reason and was not a consequence of any safety concerns.

As of 01 September 2018, 9 patients remain on treatment, 6 patients on the FGF401 single agent and 3 patients on FGF401 in combination with PDR001. This amendment will reduce the study assessments in order to ease the visit and sampling burden for these patients.

All of these patients have been on study for more than 7 cycles and are tolerating study treatment well. Their safety profiles are consistent with the overall cumulative safety data for FGF401 and PDR001. The most commonly reported AEs suspected to be related to study treatment include diarrhea, AST and ALT elevations which are thought to be on target effects of FGFR4 inhibition (refer to the current version of FGF401 IB) and will continue to be monitored for these patients.

The required study visits for patients who receive FGF401 as single agent are reduced from every 3 to every 6 weeks and the efficacy assessments are reduced from every 6 to every 12 weeks. The study visits for patients who receive FGF401 in combination with PDR001 remain the same in alignment with the PDR001 regimen of every 3 weeks and the efficacy assessments are reduced from every 6 to every 12 weeks. For all patients the basic panel of clinical laboratory parameters will be performed at each study visit. Other assessments and visits will continue to be performed at the investigator's discretion following standard of care at the site.

The central review of ECGs is no longer required and cardiac assessments may be performed at the investigator's discretion following local standard of care, since the available data and analysis of centrally reviewed ECGs collected during the study, do not indicate cardiac risk. In

[redacted]

addition, the pharmacokinetic, immunogenicity [redacted] collections will be stopped since sufficient samples have been collected for analysis to support the study objectives.

Additional changes introduced with this amendment are described below:

- The blood sample collection for the assessment of cytokines in the event of a cytokine release syndrome (CRS) was removed. In this protocol, the assessment of cytokines in the event of CRS is retrospective and is not utilized to support clinical treatment decision by study investigators. In addition, clinically assessed events of cytokine release syndrome were not reported in this study.
- To align with the EMA standard term list, the PDR001 pharmaceutical form has been updated to "Powder for solution for infusion".
- The withdrawal of consent language was revised to differentiate sample use after a patient withdraws consent based on different regulations/laws around the world.
- Other minor corrections were made for consistency and/or clarifications.

Study status

A total of 160 patients have been treated with FGF401 as single agent, 74 in the dose escalation and 86 in the Phase II part. A total of 12 patients have been treated with FGF401 in combination with PDR001; all patients were enrolled in the dose escalation part. Due to the enrollment halt, the Phase II part of the combination did not start.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Glossary of terms has been updated to add the "Personal data" term and revise the "Withdrawal of consent" term.
- Tables 6-4 and 6-5 are modified to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/toxic epidermal necrolysis (TEN) – as per the USM letter dated 15 June 2018.
- Section 6.3.2 and Table 6-5 are updated to remove the collection of blood samples for cytokines measurement.
- Section 6.6 and 6.6.6: The pharmaceutical form for PDR001 was changed to "powder for solution for infusion".
- Section 7 has been updated in all relevant sub-sections as follows:
  - New tables for reduced assessments (Table 7-1b) and for the local clinical laboratory parameters collection plan (Table 7-4b) are added.
  - Sections 7.1.4, 7.1.6 and 7.2.1 have been updated to include reduced frequency of efficacy assessments and clarify that the central collection of imaging data is not required.
  - Section 7.2.2 has been updated to remove the following assessments: height, weight, performance status, coagulation, urinalysis, [redacted], thyroid functions, cytokines and cardiac evaluations. In addition, vital signs will be performed only for patients treated with FGF401 in combination with PDR001.

[redacted]

  - Sections 7.2.3 and 7.2.4 have been updated to remove further sample collections for pharmacokinetic [redacted] assessments.
- Section 7.1.5 Withdrawal of consent language was updated.
- Section 8.2.2 and Section 8.3: The name of the Novartis Drug Safety and Epidemiology department was updated to Chief Medical Office and Patient Safety. In addition, clarification was added in the pregnancy section to specify that the follow-up of the newborn will be for 12 months.
- Section 14-4: Appendix 4 was updated to remove from Table 14-10 (Permitted concomitant medications requiring caution) duplicate records of drugs which were also listed in Table 14-9 (Prohibited concomitant medications).

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 15 June 2018. These changes are required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore they were required to have been implemented prior to IRB/IEC approval of this amendment.

All other changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 4 (06-Dec-2016)

Amendment rationale

As of 15 November 2016, the Phase I part of the study has been completed with a total of 67 patients enrolled and received different dose levels (ranging from 50mg QD to 150mg QD) of FGF401 as a single agent administered under fasted or fed conditions. The RP2D for FGF401 single agent was declared in 29 July 2016 as 120mg QD administered under fasted conditions. This decision was based on the analysis of available patients' safety, pharmacokinetic, pharmacodynamic and efficacy data. In parallel, cohorts of FGF401 administered under fed conditions are being explored at the dose level of 80mg QD and 120mg QD with no dose limiting toxicities (DLTs) observed so far. The Phase II part of the study is ongoing with 17 patients enrolled in all 3 Groups and treated with FGF401 single agent at the RP2D dose level.

The primary purpose of this amendment is to add a combination treatment of FGF401 and PDR001, a humanized anti-programmed death-1 (PD-1) IgG4 antibody, in patients with advanced hepatocellular carcinoma.

This amendment is introducing a dose escalation part, in order to identify a MTD/RP2D for the FGF401 and PDR001 combination and will be followed by a two stage Phase II part in order to further characterize the safety and evaluate the clinical activity of the combination in parallel to the FGF401 single agent. The introduction of the FGF401 and PDR001 combination treatment is based on the rationale that both FGFR4 and PD-1 inhibition have demonstrated promising anti-tumor activity in patients with HCC and that the combination will provide additional clinical benefit to patients. Emerging results from biomarker associative studies from the Phase I -FGF401 single agent available data support the removal of the FGFR4/KLB/FGF19 molecular screening selection requirement for HCC patients in the Phase II part of the FGF401 single agent. Molecular screening for these biomarkers will not be performed either for the dose escalation or the first stage of the Phase II in the FGF401 and PDR001 combination; however, based on the planned interim analysis results it may be introduced in the Stage 2-Phase II part of the combination treatment.

This amendment also introduces the collection of tumor tissue upon the development of acquired resistance to treatment. The emergence of acquired resistance to therapy is a major problem for patients with cancer. The purpose of collecting this tumor sample along with a sample of normal tissue to aid in the identification of somatic variants in the tumor is to identify genetic changes in the tumor that may underlie treatment resistance.

Furthermore, additional updates in patients' eligibility criteria and other operational aspects of the protocol are being implemented in this amendment as described below:

The laboratory values in the exclusion criteria section and other eligibility criteria for enrollment in the FGF401 single agent part have been amended to align with the eligibility requirements for the FGF401 and PDR001 combination. In addition, the laboratory values for bilirubin have been amended in order to be consistent with CTCAE version 4.03 grading and clarification was added for the coagulation parameters.

Language has been updated in the protocol to differentiate among the discontinuation of study treatment or study visits, the withdrawal of consent and the lost to follow-up patients.

[redacted]

The methods of highly effective contraception, SAE reporting and publication language of study protocol and results have been updated to reflect the most recent Novartis definitions, procedures and policies.

The list of concomitant medications that are prohibited and to be used with caution has been updated based on the latest internal drug-drug interaction guideline. The restrictions of concomitant use of acid-reducing agents, including the prohibition of proton pump inhibitors (PPI), are also removed, considering the accompanying gastric symptoms which are often seen in HCC patients. This removal is supported by the preliminary GastroPlus PBPK modeling results using the available human PK data from the FGF401 single agent-Phase I part of the study. These results suggest minimally negative impact on FGF401 exposures with PPI co-administration.

Other minor changes and corrections were made throughout the protocol for consistency and/or clarifications.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- All relevant Sections, Tables and Figures throughout the protocol were updated to include the addition of FGF401 in combination with PDR001 and to distinguish between FGF401 administered as single agent or in combination with PDR001.
- The following new sections, tables and appendices have been added for PDR001: Section 1.2.2 and Section 1.2.3-Overview of PDR001 and of the FGF401 and PDR001 combination; Section 6.1.2- Ancillary treatments; Table 6-5- criteria for interruption and re-initiation of PDR001; Section 14.9- Guidelines for immune-related Response Criteria (irRC); Section 14.11-Recommended management algorithms for PDR001-suspected toxicities.
- Section 1.2.1.2 has been updated with FGF401 clinical experience.
- Section 2-Rationale, Section 4-Study design, Section 5-Population, Section 7.1.1-Molecular pre-screening, [redacted], Section 10-Statistical Methods and data analysis and Tables 7-1 and 7-14 , have been updated to remove molecular pre-screening requirements from HCC patients (Group 1 and Group 2) in FGF401 single agent Part II.
- Specific requirements for Japan have been added in Section 5.2-Inclusion criteria and Section 7.1- Study Flow and visit schedule
- Clarification for the possibility to introduce a BID dosing regimen for FGF401 has been added in Section 4.1-Study design and Section 6.1.1-Dosing regimen.
- Section 4.1-Description of study, Tables 7-1, 7-3 and 7-4 and Section 9.3-Data collection: references to the optional companion protocol have been removed since the requirements to study the mechanisms of resistance to study treatment are now included in this amendment.
- Section 5.3- Exclusion criteria: The methods of highly effective contraception have been updated and clarification of the post-menopausal clinical profile was added. In addition, the prohibition of treatment with proton pump inhibitors (PPI) has been deleted.

[redacted]

- Section 6.4.2 and Section 6.4.3: The restrictions of concomitant use of acid-reducing agents, including the prohibition of PPI, have been removed.
- Section 7.1.4 has been updated to clarify patient's discontinuation from study treatment; new sections (Section 7.1.5 and Section 7.1.7) have been added to describe the withdrawal of consent and lost to follow-up.
- Section 8.2.2 has been updated to include clarifications on SAE reporting.
- Section 8.6-Steering Committee, has been updated to include the planned interim analysis for the Phase II part of the FGF401 and PDR001 combination.
- Section 11.5 has been updated to reflect latest procedures on the publication of study protocol and results.
- Section 14.4- list of concomitant medications that are prohibited and to be used with caution has been updated based on the latest internal DDI guideline.
- Section 14.10 has been added to include the Bayesian model used for the combination treatment.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 03

Amendment rationale

The purpose of this amendment is to add the amylase and lipase measurements to the local chemistry laboratory parameters collection plan in order to align with the criteria for dose-limiting toxicities specified in the protocol.

Changes to the protocol

Table 7-4, Local clinical laboratory parameters collection plan, has been updated to add amylase and lipase under Chemistry test category.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike-through red font for deletions~~ and red underlined for insertions.

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 02

Amendment rationale

The rationale for the amendment is to comply with the health authority suggestion to include the following:

- clarification of the starting dose planned for exploratory food effect cohort
- clarification of the prophylactic treatment with anti-emetics in cycle 1

[For Japan only]

- specification of the informed consent procedure when patient is under the age of 20 years
- specification of the additional ECG collection on Cycle 1 Day 1 for Japanese patients only

Changes to the protocol

Section 4.1, Description of study design, specifically for exploratory food effect cohort has been updated to indicate the starting dose of the fed cohort under different circumstance.

Section 6.3.3, Anticipated risks and safety concerns of the study drug, has been updated to specify the prophylactic treatment with anti-emetics is prohibited in cycle 1.

Table 7-6, Central ECG collection plan, has been updated to add additional triplicate 12-lead ECG collection at 2 hour post-dose on Cycle 1 Day 1.

Section 11.3, Informed consent procedures, has been updated to indicate the Japan specific requirement of legal representative when patient is under the age of 20 years.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike-through red font for deletions~~ and red underlined for insertions.

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 01

Amendment rationale

The rationale for the amendment is to comply with health authority request to update the definition of Grade 3 diarrhea and Grade 3 hypercalcemia based on the NCI CTCAE.

Additionally, typo corrections have been made.

Changes to the protocol

Table 6-2, Criteria for defining dose-limiting toxicities have been modified based on the CTCAE and therefore footnotes b and c have been deleted.

Table 7-9 and Table 7-10, Pharmacokinetic blood collection log for BID administration, have been updated to correct typos of dose reference ID.

Table 18-1, Criteria for interruption and re-initiation of FGF401 treatment for diarrhea management has been modified based on the CTCAE and therefore footnote b has been deleted.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike-through red font for deletions~~ and red underlined for insertions.

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths. HCC often occurs in the background of a cirrhotic liver. Most cases of HCC (approximately 80%) are associated with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections (Raza A et al 2014, El-Serag HB 2012).

Potentially curative therapies, such as surgical resection, liver transplant or other local treatments, result in survival rates of between 50-70% at 5 years for patients with early stage HCC (Llovet and Bruix 2008). However, despite advances in diagnostic techniques and increased surveillance, the majority of HCC cases present with advanced, inoperable tumors.

Untreated patients with intermediate stage HCC (multinodular asymptomatic tumors without an invasive pattern) have a median survival of 16 months. Treatment with transarterial chemoembolization (TACE), where the chemotherapy agent is directly introduced into the vessels feeding the tumor, followed by embolization, extends the median survival of this group of patients to approximately 19-20 months (Llovet and Bruix 2008).

HCC is considered to be a chemo-resistant tumor. Despite reports of partial responses to doxorubicin in a small number of patients, no clear survival advantage has been shown with this agent, and its use is limited due to its toxicity in patients with liver function impairment (Lopez et al 2006). TACE was the only treatment that had been associated with prolonged survival in intermediate HCC until the approval of the multikinase inhibitor sorafenib, which targets intracellular Raf serine/threonine kinase isoforms including Raf-1 (or C-Raf), wild-type B-Raf and mutant B-Raf and other cell surface kinases.

Two phase III studies have been published that compare sorafenib to placebo in advanced HCC patients in the first-line setting (i.e. patients with no prior systemic therapy): The “SHARP” study was conducted primarily in non-Asian countries and reported a median time to tumor progression (TTP) and overall survival (OS) of 5.5 months and 10.7 months, respectively, in the group of patients treated with sorafenib (Llovet et al 2008). The second study was conducted in Asia-Pacific region, reported median TTP and OS of 2.8 and 6.2 months, respectively (Cheng et al 2009).

The patterns of treatment for HCC are different in various parts of the world and may have accounted for the difference in OS and TTP results observed in the SHARP study and the Asia-Pacific sorafenib study.

1.2 Introduction to investigational treatments

1.2.1 Overview of FGF401

FGF401 is a Biopharmaceutics classification system (BCS) class II compound with low solubility at pH 6.8, high permeability and low to moderate food effect risk. FGF401 is a highly selective and potent FGFR4 inhibitor through binding the ATP site of FGFR4. FGF401 inhibits HCC and gastric cancer cell lines expressing FGFR4, KLB and FGF19 (triple positive) with

excellent selectivity over non-sensitive cell lines. In xenograft models, FGF401 induces regression/stasis in triple positive HCC tumors. In addition to expression by triple positive tumors, FGF19 is also induced in the ileum in response to bile acids, circulates in the human body and might stimulate the growth of the tumors expressing FGFR4 and KLB (double positive). Considering the supportive preclinical data, FGF401 provides a unique opportunity to target solid tumors and specifically HCC characterized by double or triple biomarkers positivity.

[redacted]

[redacted]

[redacted]

[redacted]

1.2.1.2 FGF401 clinical experience

This first in human study started enrollment on 29-Dec-2014. As of 30-May-2016, a total of 42 patients have been treated with FGF401 as single agent at different dose levels from 50 mg to 150 mg QD under fasted or fed (light meal) conditions.

Four DLTs were observed in three out of 33 patients that were included in the dose determining analysis set. The DLTs were: ALT increase in one patient at 50 mg QD fasted; AST increase in one patient at 150mg QD fasted; AST and ALT elevation, which was considered two-DLTs in one patient at 150mg QD fasted. The maximum tolerated dose (MTD) for FGF401 as single agent was not reached. The recommended phase II dose (RP2D) for FGF401 as single agent was determined to be 120 mg QD under fasted condition.

Overall, the most common AEs (≥ 15%) considered possibly related to FGF401 were diarrhea (66.7%), AST increase (40.5%) and ALT increase (38.1%) including Grade 3 or Grade 4 events experienced by one (2.4%), seven (16.7%) and six (14.3%) patients respectively.

Preliminary results from the dose escalation part of the study demonstrated objective responses in 3 out of 39 patients (7.69%) with HCC (2 confirmed and 1 non-confirmed partial response [PR]). None of the patients with objective responses had detectable FGF19 expression by RT-PCR. In addition, exploratory studies performed to date have not identified an association between tumor metrics and either FGF19, FGFR4, or KLB expression. These observations suggest that HCC patients have the potential to benefit from the FGF401 treatment irrespective of their FGF19, FGFR4 or KLB expression level, as measured by RT-PCR.

1.2.1.3 Clinical pharmacokinetics and metabolism

As of the PK cut-off date 04-Feb-2016, a total of 31 patients were administered FGF401 orally as a capsule at doses ranging from 50 to 150 mg QD either fed (light meal) or fasted. FGF401 was well absorbed, with Tmax ranging from 1.0 to 2.9 hours. Absorption was independent of dose and unchanged after multiple oral doses. FGF401 has a short to moderate T1/2, which ranged from 3.9 to 7.5 hours, and also appeared to be independent of dose and time. Plasma drug exposure of FGF401 increased with increasing doses with a trend toward under proportionality. Drug accumulation of FGF401 following multiple dosing was minimal. No substantial exposure difference was observed in clinic between fed (light meal) and fasted cohorts at 80 mg.

The plasma concentrations of FGF401 within a steady-state dosing interval almost all exceeded the preclinical in vivo pFGFR4 IC90 value, as well as the in vitro cellular pFGFR4 IC90 at the starting dose of 50 mg.

[redacted]

Human metabolism, excretion and clinical drug-drug interaction studies have not yet been performed. [redacted]

1.2.2 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody that blocks the binding of Programmed Death- Ligand 1 (PD-L1) and Programmed Death Ligand-2 (PD-L2) to Programmed Death-1 (PD-1). PDR001 recognizes PD-1 in cynomolgus monkeys and shows functional activity *in vitro/ex vivo*.

[redacted]

1.2.2.2 PDR001 Clinical experience

The first in human phase I/II study [CPDR001X2101] started enrollment on 27 April 2015 and is ongoing in patients with advanced malignancies. The dose escalation part of the study was completed with a total of 58 patients treated at the dose levels of 1, 3 and 10 mg/kg every two weeks and 3 and 5 mg/kg every four weeks. No patient experienced a DLT. The PK analysis of the dose escalation data using a population approach and the expected wide therapeutic index of PD-1 inhibitors support the use of flat dosing for PDR001 of 400 mg every four weeks or 300 mg every three weeks (Q3W). The expected PDR001 Ctrough concentrations using either dosing regimen exceed the EC50 for PD-1 blockade by approximately 75-fold in an ex vivo assay in peripheral blood mononuclear cells (PBMCs). Based on the available PK and safety data, the RP2D of PDR001 has been declared as 400 mg i.v. every four weeks or 300 mg i.v. Q3W for combination treatment regimens for which this may be more convenient.

[redacted]

PDR001 is currently being studied alone or in combination with other agents in ongoing phase I/Ib/II clinical trials. The preliminary toxicity profile appears to be similar to that of marketed inhibitors of PD-1 including the type, severity and frequency of occurrence of immune-mediated adverse events. As observed with other PD-1 inhibitors, immune-mediated toxicities observed with PDR001 are reversible in many cases. In some cases, they may require treatment with corticosteroids. Certain toxicities are expected to be lifelong and may require replacement therapy with hormones, for example in the case of hypothyroidism. The most frequent suspected AEs (data cut-off: 17-Dec-2015) included diarrhea (8 patients, 13.8%), fatigue (8 patients, 13.8%), nausea (6 patients, 10.3%), hypothyroidism (5 patients, 8.6%), pruritus (5 patients, 8.6%), vomiting (4 patients, 6.9%), anemia (3 patients, 5.2%), constipation (3 patients, 5.2%), decreased appetite (3 patients, 5.2%), dry mouth (3 patients, 5.2%) and maculopapular rash (3 patients, 5.2%).

Based on the preliminary data, PDR001 was well tolerated with a safety profile similar to those of other marketed anti-PD-1 antibodies.

[redacted]

1.2.3 Overview of FGF401 and PDR001

1.2.3.1 Non clinical and clinical experience with the FGF401 and PDR001 combination

There is no experience with this combination in the non-clinical and clinical setting.

1.2.3.2 Potential of drug interactions

Specific studies to investigate DDI have not been conducted with FGF401 and PDR001. As an antibody, PDR001 is eliminated through protein catabolism and target-mediated disposition. Cytokines produced by activated lymphocytes may impact the levels of Pgp and the activity of P450 enzymes. The clinical relevance of cytokines impacting levels of Pgp and P450 with administration of PDR001 is unknown but considered unlikely. FGF401 is a small molecule eliminated mainly by hepatic metabolism with both phase I and II enzymes involved. Pharmacokinetic DDI between FGF401 and PDR001 is therefore not expected.

1.2.3.3 Potential overlapping toxicities

From the preclinical safety profile of FGF401 and PDR001 no overlapping target organ toxicity is expected. However, preliminary clinical data from the ongoing single agent CFGF401X2101 study suggests that FGF401 associated toxicities may overlap with those of PD-1 inhibitors including PDR001 observed in the clinic.

Potential overlapping toxicities include diarrhea and increased AST/ALT, which have been reported for PD-1 inhibitors including PDR001. Lipase increase is another potential overlapping toxicity, which although not reported for PDR001, has been reported for other PD-1 inhibitors.

[redacted]

2 Rationale

2.1 Study rationale and purpose

FGF19 has unique specificity for FGFR4. In addition, cellular co-expression of KLB is required for FGF19 binding to FGFR4 and for the subsequent intracellular signaling. Therefore, the distribution and the relative levels of FGFR4 and KLB dictate the organ/tumor of FGF19 action (Lin et al 2007, Lin et al 2012).

FGF19-FGFR4 pathway plays an important homeostatic physiological role in the regulation of bile acid homeostasis. The expression of FGF19 is induced in the ileum in response to bile acids that are released into the intestinal lumen after feeding. FGF19 then circulates to the liver where FGFR4 and KLB are highly co-expressed to suppress CYP7A1, the rate-limiting enzyme for bile acid synthesis. FGF19 also limits bile acid release into the intestine by triggering gallbladder filling. In this manner, FGF19 serves as a key regulator in the postprandial negative feedback loop modulating bile acid synthesis and release (Lin et al 2012, Mellor 2014).

Recent data suggests that the FGF19-FGFR4 signaling network may be a key driver in certain forms of HCC, making the pathway an interesting, emerging molecular target for potential therapeutic intervention (Ho et al 2009, Miura et al 2012, Poh et al 2012).

In vivo, the ectopic expression of FGF19 in the skeletal muscle in mice promotes hepatocyte proliferation and induces HCC formation in a paracrine fashion (Nicholes et al 2002) and an anti-FGF19 monoclonal antibody prevents tumor formation (Desnoyers et al 2008). Further, when FGF19 transgenic mice were bred with FGFR4 knockout mice, they failed to develop liver tumors highlighting the relevance of FGFR4 in FGF19-driven HCC (French et al 2012).

Several publications [redacted] that FGF19 aberrant expression, occurring as a consequence of focal gene amplification (11q13) or by some other yet unknown mechanism, occurs in subsets of HCCs, where FGFR4 and KLB are also co-expressed. In this setting, FGF19 leads to constitutive FGFR4 activation by acting in an autocrine fashion (Sawey at el 2011; Guagnano et al 2012).

Other publications indicated that a subset of HCC patients characterized by elevated FGFR4 and/or FGF19 expression in the tumors have a poorer prognosis and might be amenable to anti-FGFR4 therapy (Ho et al 2009, Miura et al 2012, Poh et al 2012).

FGF401 is a highly selective and potent FGFR4 inhibitor, which will be developed in patients with HCC or other solid malignancies characterized by positive expression of FGFR4 and KLB. The initial clinical strategy for the FGF401 development was driven by the following assumptions:

1. Clinical activity of FGF401 will be restricted to patients with double ($FGFR4^+$ and KLB^+) or triple ($FGFR4^+$ and KLB^+ and $FGF19^+$) positive solid tumors, and it is assumed that HCC will account for >95% of the patients enrolled in the phase I. The incidence of double positivity in other solid tumors is very low (1-2%).Within the HCC patient population however, approximately 30-40% of tumors are double positive and around 10-15% are triple positive.
2. FGF19 secreted from non-tumor cells, e.g. ileum, stromal cell, might stimulate the growth of the double positive tumors and it might act as a growth factor in triple positive tumors.

[redacted]

Preliminary results from the dose escalation part of this study demonstrated objective responses in 3 out of 39 patients (7.69%) with HCC (2 confirmed and 1 non-confirmed PR). [redacted] hese observations suggest that HCC patients have the potential to benefit from the FGF401 treatment irrespective of their FGF19, FGFR4 or KLB expression level, as measured by RT-PCR.

Additionally, preliminary results showing objective clinical activity in 2 out of 8 patients (1 unconfirmed PR and 1 stable disease [SD]) were recently reported in a clinical study with another FGFR4 inhibitor in advanced HCC patients. These patients were FGF19 positive by IHC (Kim ENA 2016). Collectively these data further implicate the FGFR4 pathway as a driver in HCC and suggest that the FGFR4 inhibition may have a role in the treatment of HCC.

Recent clinical studies have highlighted the potential of targeting the PD-L1/PD-1 pathway in HCC. A phase I/II study of Nivolumab, a monoclonal antibody that results in PD-1 checkpoint inhibition, showed durable responses in advanced HCC; the objective response rate was 16% and the 9-month overall survival rate was 71% (Bruno ASCO 2016). This study also suggested that Nivolumab has a manageable safety profile in HCC, including in those patients with HBV and HCV infections.

Together, these clinical results suggest that the combined inhibition of the FGFR4 signal with FGF401 and the inhibition of PD-1 with the checkpoint inhibitor PDR001 may lead to additional clinical benefit for patients with advanced HCC.

In this study the safety and clinical activity of the FGF401 and PDR001 combination will be evaluated in parallel to FGF401 single agent, in an unselected HCC population. Associative studies of immunomodulatory and FGF pathway expression changes in tumor and blood samples with clinical outcome will be retrospectively explored.

2.2 Rationale for the study design

2.2.1 FGF401 single agent

Phase I part

The design of the phase I, open label, dose finding part was chosen in order to establish the MTD and/or RP2D of FGF401 in patients with HCC or solid tumors characterized by positive expression of FGFR4 and KLB. The dose escalation will be guided by a Bayesian hierarchical logistic regression model (BHLRM). This model estimates the relationship between dose and the probability of a patient experiencing a DLT in fasted condition (stratum 1) and in fed condition (stratum 2). The BHLRM will allow for both full exchangeability between the strata parameters and non-exchangeability between strata parameters. In this way the model has the flexibility to allow for both the case in which the dose-toxicity relationship is similar for the two strata, and the case in which the relationship is different for each. In the event that the relationship is similar, then the model structure will allow borrowing of information between the two strata, which will in turn lead to improved estimation of the dose-toxicity relationship.

[redacted]

This model is a hierarchical adaptation of the Bayesian logistic regression model (BLRM), a well-established method to estimate the MTD and/or RP2D in cancer patients. The BHLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA ("Guideline on clinical trials in small populations", February 1, 2007) and endorsed by numerous publications (Babb et al 1998, Neuenschwander et al 2008, Bailey et al 2009), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

The decisions on new dose levels are made by the Investigators and Novartis study personnel and will be based upon the recommendations made by the BHLRM, patient tolerability and safety, PK, [redacted] and efficacy information available at the time of the decision (Section 6.2.3).

Phase II part

Once the MTD and/or RP2D has been defined, a phase II part will open at the MTD or RP2D to further characterize safety, anti-tumor activity and PK profile of FGF401 at this dose. The phase II part will include 3 Groups as summarized in Figure 4-1, each having specific enrollment criteria.

Group 1 will enroll HCC patients from Asian countries

Group 2 will enroll HCC patients from non-Asian regions

Group 3 will enroll patients with other solid malignancies regardless of the geography

Epidemiology and preclinical data supports the feasibility and activity of FGF401 in HCC patients, respectively. Considering that the treatment guidance for HCC (specifically the locoregional treatments such as percutaneous hepatic arterial embolization, radiofrequency ablation, and percutaneous interventional therapy) are different in various parts of the world reflected in the difference in OS and TTP results observed in the SHARP study and the Asia-Pacific sorafenib studies, subgrouping based on the geography and corresponding patterns of treatment will be implemented in this study. The HCC patients recruited in Asian countries will be enrolled in Group 1 and the HCC patients from non-Asian regions will be enrolled in Group 2.

For Japan, the epidemiology pattern of hepatitis viral infection (HCV infections) is more similar to the non-Asian regions instead of other Asian countries (HBV infections) (Bosch et al 2004). However, the patterns of treatment for locally or advanced HCC may account for the difference in efficacy results. In some clinical studies, Japan has been stratified into the Asian group due to the similarity in term of locoregional treatment (number of TACE) (Lencioni et al 2012, Johnson et al 2013). In this study, considering the relevance of the locoregional treatment, Japan will be sub grouped into Group 1 (Asian patients).

Group 1 and Group 2 will focus on characterizing the activity and tolerability of FGF401 in HCC patients irrespective of their FGFR4, KLB and FGF19 expression.

Group 3 will focus on characterizing the activity and tolerability of FGF401 in any other solid tumor patients with double positive expression. Preclinical data supports the activity of FGF401 in one of the gastric cancer cell lines and may potentially work on other tumor types based on the mechanism described in Section 2.1.

[redacted]

Exploratory food effect cohort

[redacted]. Within the phase I part, the exploratory food effect cohort(s) will be included to assess the effect of food uptake on FGF401 PK properties and safety profiles in the patients.

According to the human physiology, when a meal is ingested, gallbladder emptying occurs and delivers bile acids to the small intestinal lumen. This physiological release of bile acids might be increased by FGF401 administered under fed condition. Therefore, the food effect exploration coupled with laboratory analysis described in Table 7-1 will also help to understand the food effect on [redacted] AEs under different feeding conditions.

2.2.2 FGF401 in combination with PDR001

Phase I part

The design of the phase I, open label, dose finding part was chosen in order to characterize the safety and tolerability of FGF401 in combination with PDR001 in patients with advanced HCC and determine a RP2D or MTD. The dose escalation will be guided by a Bayesian Logistic Regression Model (BLRM). The use of Bayesian response adaptive models is a well-established method to estimate the MTD and/or RP2D in cancer patients as described above and in Section 6.2.3.

Phase II PartThe Phase II part of the FGF401 in combination with PDR001 will start once a MTD and/or RP2D is identified. This part has a staged study design. Initially the study will enroll HCC patients without molecular selection. If the clinical activity in this unselected population is below the pre-defined target range, the clinical activity will be further evaluated in sub-groups of patients, based upon FGF19 expression and/or FGF19 pathway activation to inform next decisions for clinical development (see Section 4.2). This design provides the opportunity to evaluate the combination in a molecular pre-selected HCC population, should the combination have limited activity in an unselected population. Considering the difference in OS and TTP results observed in the SHARP study and the Asia-Pacific sorafenib studies, sensitivity analyses by geographic region will be explored.

2.3 Rationale for dose and regimen selection

The starting dose and regimen of FGF401 single agent is 50 mg once daily based on the preclinical safety and tolerability data. [redacted]

[redacted]

For the dose escalation part of the FGF401 and PDR001 combination, the starting dose is 80mg QD for FGF401 and 300mg Q3W for PDR001.

The RP2D for single agent FGF401 is 120mg QD administered under fasted condition. The dose of 80mg QD for FGF401 was selected for the combination as it is one dose level below the RP2D.

The dose of 300mg Q3W for PDR001, as a flat fixed dose, was selected as this is the RP2D for single agent PRD001 declared in the [CPDR001X2101] study.

The selected starting dose of FGF401 on a continuous daily schedule in combination with the fixed dose of PDR001 administered every 3 weeks is supported by the risk assessment. This includes that the starting dose meets the EWOC with the new combination BLRM that leverages single agent FGF401 and PDR001 dose-DLT data. Although pharmacokinetic DDI between FGF401 and PDR001 is not expected (Section 1.2.3.2), the exposure of FGF401 and PDR001 will be monitored in the study to assess any potential DDI.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
Phase I part To estimate the MTD and/or RP2D of FGF401 single agent and in combination with PDR001	Incidence rate and characteristics of DLT during the first cycle of dosing for FGF401 single agent and during the first two cycles of dosing for FGF401 in combination with PDR001	
Phase II part To investigate the anti-tumor activity ofFGF401 single agent and in combination with PDR001	FGF401 single agent: Group 1 and Group 2: Time to progression (TTP); Group 3: Overall response rate (ORR), based on local assessment per RECIST v1.1 FGF401 in combination with PDR001: ORR based on local assessment per RECIST v1.1.	
Secondary (Phase I and II part)		Refer to Section 10.5
To characterize the safety and tolerability of FGF401 single agent and in combination with PDR001	Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs Tolerability: Dose interruptions and reductions	Refer to Section 10.5.2
To further investigate the anti-tumor activity of FGF401 single agent and in combination with PDR001	**Phase I part** BOR, ORR, DCR, TTP and OS, based on local assessment per RECIST v1.1 for FGF401 single agent or RECISTv1.1. and irRC for the FGF401 and PDR001 combination **Phase II part- FGF401 single agent** Group 1 and Group 2: BOR, ORR, OS and DCR, based on local assessment per RECIST v1.1 Group 3: BOR, DCR, OS and PFS, based on local assessment per RECIST v1.1 **Phase II part- FGF401 and PDR001 combination** TTP, PFS, OS, BOR, DOR and DCR, based on local assessment per RECIST v1.1. and irRC	Refer to Section 10.5.1
To characterize the PK properties of: -FGF401 single agent and in combination with PDR001 -PDR001 in combination with FGF401	Plasma concentration of FGF401, PDR001 and PK parameters including but not limited to C_{max}, C_{min}, AUC_{inf}, AUC_{last}, AUC_{tau} and $T_{1/2}$	Refer to Section 10.5.3
To assess immunogenicity of PDR001	Presence and/or concentration of anti-PDR001 antibodies	Refer to Section 10.5.3

[redacted]

Objective	Endpoint	Analysis
Phase I part- FGF401 single agent To evaluate food effect on FGF401 exposure and safety profile	● Plasma concentration of FGF401 and PK parameters when dosing under fed condition ● Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs when dosing under fed condition	Refer to Section 10.5.3.2.3

[redacted]

[redacted]

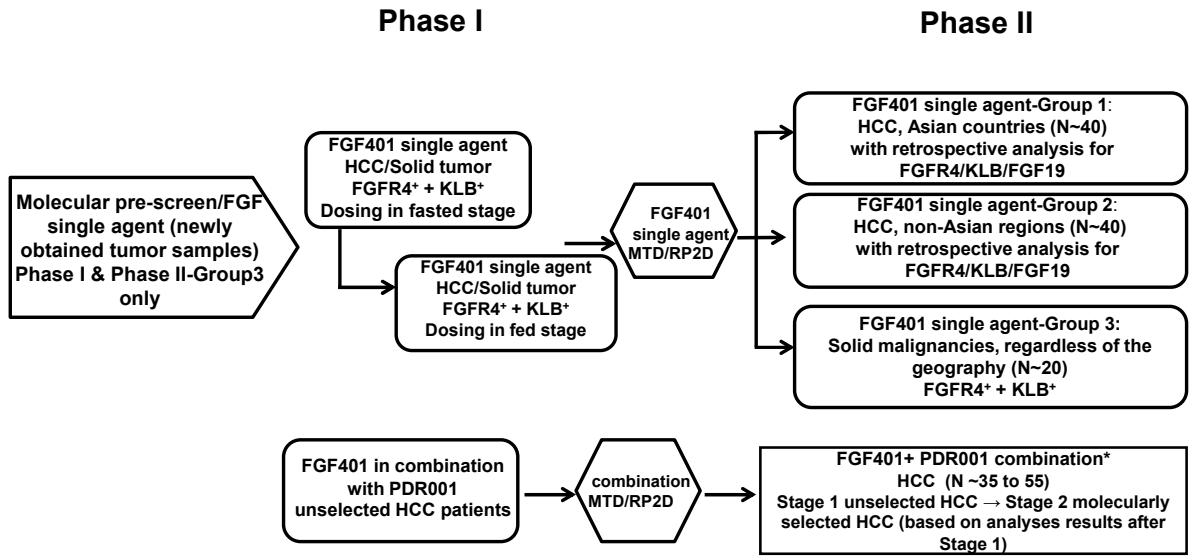
4 Study design

4.1 Description of study design

This study has been designed as a phase I/II, multi-center, open-label study starting with a phase I dose escalation part followed by a phase II dose expansion part. The study treatment will be taken until patient experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the investigator or patient's withdrawal of consent. Figure 4-1 summarizes the study design overall while Figure 4-2 provides additional details for the study design for the FGF401 and PDR001 combination.

FGF401 will be administered on a continuous once daily (QD) dosing regimen for both FGF401 single agent and in combination with PDR001 parts. However, based upon emerging FGF401 clinical safety, efficacy and related exposure-response analysis data, the FGF401 dose regimen may change from QD to BID at any time during the study for all newly enrolled patients.

Figure 4-1 Study design



*refer to Figure 4-2 for additional details

4.1.1 FGF401 single agent

Phase I part

In the phase I part, patients with HCC or other advanced solid tumors characterized by positive FGFR4 and KLB expression will be enrolled. Patients will be tested for the expression of FGFR4 and KLB in the molecular pre-screening of this study to confirm the eligibility, refer to Section 7.1.1 for details. A BHLRM with EWOC will guide the dose escalation to determine the MTD and/or RP2D. At least 21 evaluable patients should be treated in the phase I part, for the model to have reasonable operating characteristics relating to its MTD and/or RP2D recommendation. If significant activity is seen early in the phase I dose escalation, then a recommended dose may be identified and the phase II Groups may be initiated without determination of the MTD; therefore fewer than 21 patients may be required.

Phase II part

Once the MTD and/or RP2D is declared, additional patients with advanced HCC or other solid tumors bearing positive FGFR4 and KLB expression will be enrolled into 3 Groups to assess the preliminary anti-tumor activity of FGF401 in Phase II dose expansion part. HCC patients will be enrolled irrespective of the FGFR4 and KLB expression which will be analyzed retrospectively. For patients with other solid tumors, positive FGFR4 and KLB expression is required for enrollment. HCC patients recruited in Asian countries will be enrolled in Group 1; HCC patients from non-Asian regions will be enrolled in Group 2; patients with other solid malignancies regardless of the geography will be enrolled in Group 3.

Each group within the phase II dose expansion part will target a different number of patients. Details of the sample size calculations leading to the patient numbers are provided in Section 10.8. Group 1 and Group 2 will enroll around 40 patients each and Group 3 will enroll approximately 20 patients.

Exploratory food effect cohort

Within the phase I part, the exploratory food effect cohort(s) will be included to assess FGF401 PK properties, safety and tolerability in patients under fed conditions. This food effect cohort will start when [redacted] clinical activity is observed and will be conducted in parallel with the phase I fasted dose escalation. If at this time, the MTD under the fasted condition has not been declared yet, the starting dose of the fed cohort will be equal or lower than the highest dose shown to be tolerated during the first cycle in the cohort of fasted patients. If at this time, the MTD under fasted conditions has been declared, the starting dose of the fed cohort will be lower than the MTD under the fasted condition. For both scenarios, the starting dose of the fed cohort will satisfy the escalation with overdose control (EWOC) criterion. The fed dose escalation will be guided by a BHLRM. The decision to continue with fed and/or fasted condition in the phase I and phase II part(s) will be made by the Investigators and Novartis study personnel based on the tolerability, safety profile, PK, PD and efficacy information available at the time of the decision. The dosing regimen and administration requirements are outlined in Section 6.1.1.

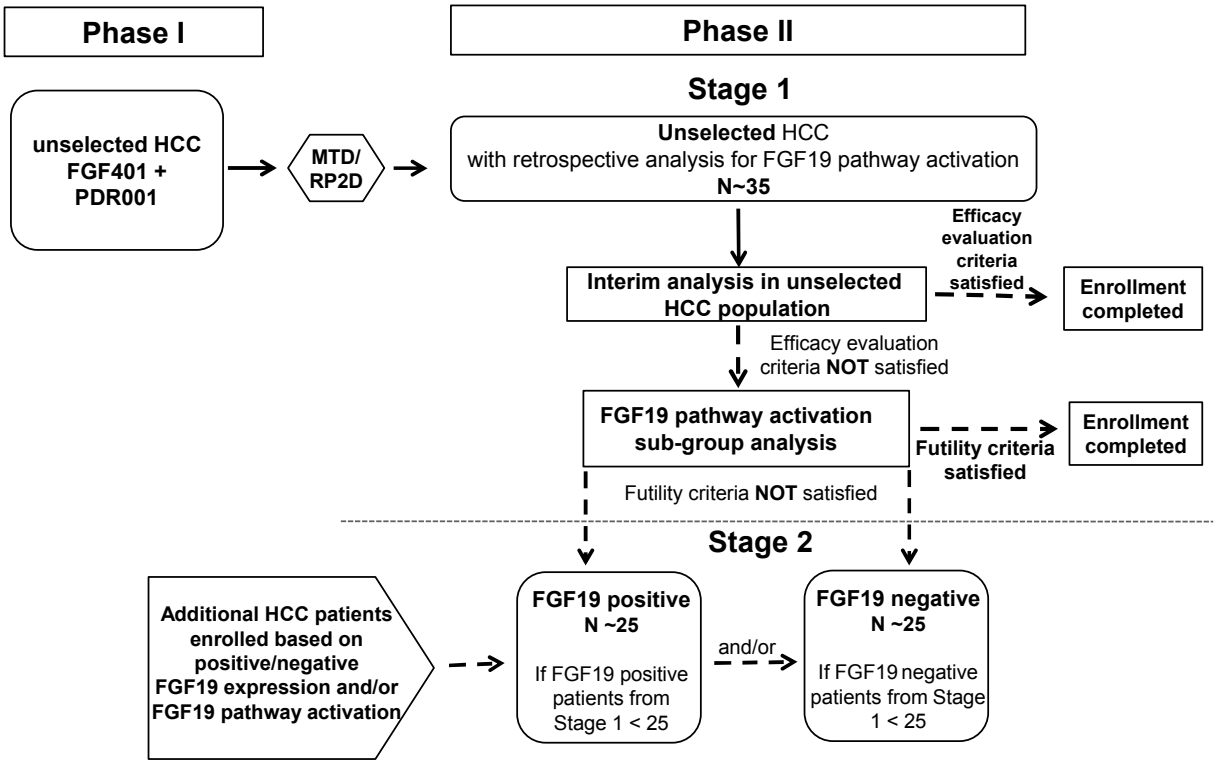
PK samples will be collected following the same PK collection schedule selected for the phase I part of the study (refer to Table 7-7 and Table 7-9).

[redacted]

4.1.2 FGF401 in combination with PDR001

Figure 4-2 summarizes the study design for FGF401 in combination with PDR001.

Figure 4-2 Study design- FGF401 in combination with PDR001



Phase I part

In the Phase I part cohorts of patients will be treated with FGF401 in combination with a fixed dose of PDR001 until the MTD is reached or a recommended Phase II dose is established. The FGF401 dose will be increased and the PDR001 dose will remain constant. For each untested dose level the administration of the first dose of the study treatment will be staggered by 24 hours for the first three patients. The dose escalation will be guided by a BLRM following the EWOC principle. A minimum of 12 patients are required in the phase I part for the model to have reasonable operating characteristics to determine the MTD of FGF401 in combination with PDR001. If significant activity is seen early in the phase I dose escalation, then a recommended dose may be identified and the phase II part may be initiated without determination of the MTD; therefore fewer than 12 patients may be required.

Phase II part

The Phase II part of this study has a 2-stage design. In Stage 1, approximately 35 HCC patients will be enrolled without molecular selection (e.g. irrespective of their FGFR4, KLB or FGF19 expression). Upon completion of the Stage 1 enrollment, an interim analysis will be performed to assess the clinical activity in this population. The phase II part will be stopped at Stage 1, if the criteria for substantial efficacy as described in Section 4.2 and Section 10.7.2 are met.

[redacted]

Should these criteria not be met, sub-group analysis, based upon FGF19 expression and/or FGF19 pathway activation will be performed.

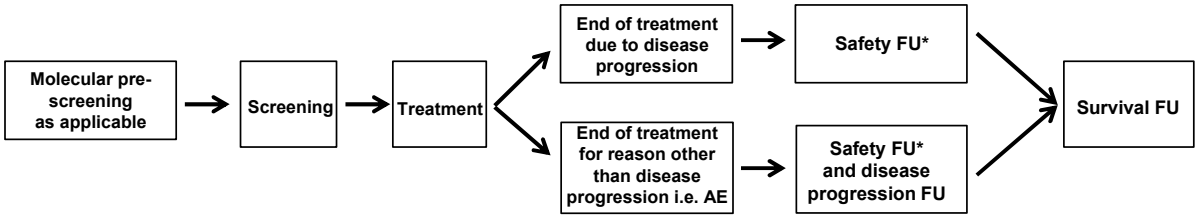
Based on the futility criterion specified in Section 4.2 and Section 10.7.2, if the efficacy in a sub-group is insufficient, no further patients will be enrolled to that subgroup. Otherwise, enrollment will continue until a total of approximately 25 patients are identified for the specific sub-group(s) in order to further assess the efficacy. At this time, molecular pre-screening will be employed in order to identify the appropriate molecular sub-group(s).

The sub-group analysis will be based upon FGF19 pathway expression and/ or activation. The molecular sub-group will be defined based upon emerging molecular data and associative analyses of the FGF401 single agent parts of the study and the definition for each sub-group will be available at the time of the interim analysis. If based on these associative studies, a molecular sub-group is not identified, patient enrollment will not continue beyond Stage 1.

Study visit flow

The study includes different periods starting by Molecular pre-screening (applicable only for Phase I and Group 3 in Phase II of FGF401 single agent and at Stage 2 of FGF401 and PDR001 combination should it proceed), Screening, Treatment, End of Treatment, Disease progression follow-up (if applicable), Safety follow-up (refer to Section 7.1.6) and then ended by Survival follow-up period (Figure 4-3).

Figure 4-3 Study Flow



*Refer to Section 7.1.6 for additional details.

4.2 Timing of interim analyses and design adaptations

No formal interim analysis will take place in the FGF401 single agent part.

In the phase I parts of this study for both FGF401 single agent and FGR401 in combination with PDR001, the MTD and/or RP2D will be determined based on available safety, tolerability, PK, [redacted] and efficacy data, guided by the recommendations from the Bayesian model using EWOC criterion and participating investigators. The phase II part will then begin as specified in Section 4.1. Details about the timing of data monitoring can be found in Section 8.5 and Section 10.7.

In the Phase II part of the FGF401 in combination with PDR001, a 2-stage design with interim efficacy evaluation of this combination treatment in HCC patients will be used. Stage 1 will initially enroll approximately 35 HCC patients irrespective of their FGFR4, KLB or FGF19 expression status. An interim analysis of efficacy will be performed after the first 35 patients have been enrolled and have had at least one-post treatment tumor evaluation or discontinued earlier (Stage 1). Interim decision making will be primarily based on the estimation of ORR

[redacted]

based on local assessment per RECIST v1.1. Based on the interim efficacy evaluation, the phase II part will not be continued after Stage 1 if the posterior probability of ORR in the unselected population included in the no/limited anti-tumor activity interval [0, 0.15) is less than 0.10 and the posterior median ORR is 0.30 or more. Considering the exploratory nature of the study, when the aforementioned criteria are not met but the evaluation of overall efficacy and safety suggests that the treatment is promising for further development, decision to stop at Stage 1 for success can also be made by Novartis.

Should the efficacy criteria not be met, go/no go decision to Stage 2 will be made by evaluating the anti-tumor activity in subgroups defined by the FGF19 expression and/or FGF19 pathway activation based on the predictive probability of ORR. If a subgroup(s) satisfies the criterion that the predictive probability to not meet the efficacy criteria (i.e. posterior probability of ORR included in the no/limited anti-tumor activity interval is less than 0.10 and the posterior median ORR is 0.30 or more) at the final analysis is not greater than 0.90, and the number of patients in that subgroup is less than 25, the study will move to Stage 2 and further enrollment to that subgroup will be permitted until a total number of approximately 25 patients is reached to further characterize efficacy within that subgroup. If 25 or more patients are already enrolled to the subgroup, interim analysis will be performed but no further enrollment will be allowed in that subgroup.

4.3 Definition of end of the study

The study will end when the treatment period, safety follow-up, disease progression follow-up and survival follow-up have been completed for all patients as described in Section 7.1.6, or when the study is terminated early.

Completion of the survival follow-up period will occur once a minimum of 80% of patients in the phase II part of both FGF401 single agent and FGF401 in combination with PDR001 have died, have been lost to follow-up, or have been followed for survival for minimum 18 months after receiving the first dose of study treatment, whichever is sooner see Section 7.1.6.

See Section 10 Statistical Methods and Data Analysis for details of timing of the primary analysis and final reporting of data.

The disease and survival follow-up evaluations might not be completed in case Novartis decides to stop enrollment prematurely. In such cases, end of study will be when the treatment period and the safety follow-up have been completed for all patients.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for an End of Treatment (EOT) visit, and the assessments for EOT as described in Section 7.1.4 should be performed for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

[redacted]

5 Population

5.1 Patient population

The phase I part of this trial with oral FGF401 as single agent will be conducted in adult patients with hepatocellular carcinoma or other solid malignancies characterized by positive FGFR4 and KLB expression. The phase II part will include 3 Groups as summarized in Figure 4-1.

FGF401 in combination with PDR001 will be administered in adult patients with advanced HCC.

The expression of FGFR4, KLB and FGF19 will be tested by a Novartis designated laboratory, see Section 7.1.1 and Section 7.2.4.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any procedures that are not considered standard of care. [**For Japan only:** written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.**]**
2. Patients (male or female) ≥ 18 years of age
3. ECOG Performance Status ≤ 1
4. Presence of at least one measurable lesion according to RECIST v1.1 (see Section 14.1). For HCC patients, lesions previously treated with loco-regional therapy, such as radiation therapy, hepatic arterial embolization, radiofrequency ablation, and percutaneous interventional therapy should not be considered measurable unless progression is noted at baseline.
5. Patients must have a site of disease amenable to biopsy and be suitable and willing to undergo the study's required biopsies according to treating institution's guidelines and requirements for such procedures.

6. **Inclusion criteria specific for FGF401 single agent** Patients with confirmed positive expression of FGFR4 and KLB at molecular pre-screening for Phase I and Phase II-Group 3. The biomarker positivity will be defined by a Novartis designated laboratory. Patients with FGFR4 mutations can be enrolled in the study following discussion and agreement with Novartis.
7. **Phase I part:**
    a. Patients with HCC or advanced solid tumors, who have progressed despite standard therapies, are intolerant of standard therapy, or for whom no standard therapy exists.
    b. For HCC patients:
        a. Diagnosis of advanced HCC according to the AASLD Guidelines
        b. HCC stage C according to the BCLC staging classification

[redacted]

c. Current cirrhotic status of Child-Pugh class A (5-6 points), with no encephalopathy and/or ascites. Child-Pugh status must be calculated based on clinical findings and laboratory results during the Screening period.

8. **Phase II part**:
   a. Group 1: HCC patients from Asian countries
   b. Group 2: HCC patients from non-Asian regions

      For Group 1 and 2:

      a) Diagnosis of advanced HCC according to the AASLD Guidelines
      b) HCC stage C according to the BCLC staging classification
      c) Prior systemic treatment with sorafenib for advanced HCC with documented disease progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment. Specifically, this can be defined as:

      - Documented radiological confirmation (radiology scans or report) of disease progression during or after sorafenib treatment. [For France only: patients must have received at least 8 weeks of prior sorafenib treatment.]
      - Intolerance to sorafenib (at any dose and/or duration) is defined as documented sorafenib-related Grade 3 or 4 adverse events that led to sorafenib discontinuation.

      d) Current cirrhotic status of Child-Pugh class A (5-6 points), with no encephalopathy and/or ascites. Child-Pugh status must be calculated based on clinical findings and laboratory results during the Screening period.

   c. Group 3: Patients with other advanced solid tumor
      a) Patients have progressed despite standard therapies, are intolerant of standard therapy, or for whom no standard therapy exists.

Inclusion criteria specific for FGF401 in combination with PDR001

9. Patients with HCC as defined below:
   a. Diagnosis of advanced HCC according to the AASLD Guidelines
   b. HCC stage C according to the BCLC staging classification
   c. Current cirrhotic status of Child-Pugh class A (5-6 points), with no encephalopathy and/or ascites. Child-Pugh status must be calculated based on clinical findings and laboratory results during the Screening period
10. Patients who have received up to 2 previous lines of systemic treatment for advanced HCC and one treatment must have included sorafenib with documented disease progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment. Specifically, this can be defined as:
    - Documented radiological confirmation (radiology scans or report) of disease progression during or after sorafenib treatment. [For France only: patients must have received at least 8 weeks of prior sorafenib treatment.]
    - Intolerance to sorafenib (at any dose and/or duration) is defined as documented sorafenib-related Grade 3 or 4 adverse events that led to sorafenib discontinuation.
11. For Phase II-Stage 2: Documented FGF19 expression level and/or FGF19 pathway activation by a Novartis designated laboratory.

[redacted]

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Previous treatment with a selective FGF19-FGFR4 targeted therapy and/or pan-FGFR inhibitor.
2. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral FGF401 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, small bowel resection).
3. Patient have received prior therapies within the following time frames prior to the first dose of study treatment:
   a. For HCC patients in Phase II (FGF401 single agent) :
      - previous systemic anti-cancer therapy other than sorafenib
      - last dose of sorafenib therapy ≤ 2 weeks from study treatment start
      - any other anti-cancer therapy (including locoregional therapy e.g. hepatic arterial embolization, radio-frequency ablation, radiation therapy) after disease progression during or after sorafenib treatment with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain.
   b. For HCC patients in FGF401 combination with PDR001:
      - last dose of systemic anti-cancer therapy with sorafenib: ≤ 2 weeks or
      - unconjugated monoclonal antibody therapies ≤ 6 weeks or 5 half-lives, whichever is shorter
      - last dose of conventional cytotoxic chemotherapy: ≤ 2 weeks (≤ 6 weeks for nitrosoureas and mitomycin-C)
      - any other anti-cancer therapy (including locoregional therapy e.g. hepatic arterial embolization, radio-frequency ablation, radiation therapy) after disease progression during or after last systemic treatment with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain.
   c. For other solid tumor patients:
      - The last dose of conventional cytotoxic chemotherapy: ≤2 weeks (≤6 weeks for nitrosoureas and mitomycin-C)
      - Biological therapy (e.g., antibodies): ≤6 weeks
      - Non-cytotoxic small molecule therapeutics (e.g., sorafenib): ≤5 half-lives or ≤2 weeks (whichever is longer)
      - Previous wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks and limited field radiation for palliation ≤ 2 weeks
      - Participation in a prior investigational study within 7 days or within 5 half-lives of the investigational product, whichever is longer

   Note: exceptions to the above prior therapy timeframes are possible, on a case by case basis, following discussion and mutual agreement between Investigator and Novartis.
4. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred

[redacted]

within 3 years prior to study entry; completely resected basal cell and squamous cell skin cancers and completely resected carcinoma in situ of any type.

5. Symptomatic CNS metastases which are neurologically unstable, or CNS metastases requiring local CNS directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within 2 weeks of first dose of study treatment.

   Note: Patients with controlled CNS metastases may participate in this trial. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on CNS imaging for 4 weeks and before receiving the first dose of study treatment and not requiring steroid therapy for at least two weeks before receiving the first dose of study treatment.
6. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures. Any severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.
7. Ongoing active diarrhea requiring medications (e.g. bile acid sequestrant (BAS), loperamide)
8. Irritable bowel syndrome with signs/symptoms or requires medications
9. Current evidence of calcium-phosphate homeostasis impairment, defined as:
   a. Inorganic phosphorus > 5.5 mg/dL
   b. Total calcium > 11.5 mg/dL
   c. Ionized serum calcium > 1.5 mmol/L
   d. Patients with current evidence of endocrine alteration of calcium/phosphate homeostasis, e.g. parathyroid disorders, tumor lysis, tumoral calcinosis etc.
10. Patient having out of range laboratory values defined as:

    Hematology
    a) Hemoglobin < 9 g/dL (SI Units: 90 g/L)
    b) Platelet count < 75000/mm^3
    c) Absolute neutrophil count (ANC) < 1500/mm^3

    Chemistry
    a) Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
    b) AST or ALT > 3 x ULN
    c) Serum creatinine > 1.5 x ULN or creatinine clearance (calculated using the Cockcroft-Gault formula or measured) < 40 mL/min

    Coagulation: PT > 4 seconds more than the ULN or INR > 1.7
11. Patients receiving treatment with CYP1A2, CYP2C9 and CYP3A4/5 substrates with a narrow therapeutic index (NTI) that cannot be discontinued for the duration of the study (refer to Appendix 4).
12. [redacted]

13. Patients receiving known BSEP efflux transporter inhibitors that cannot be discontinued 3 days prior to the start of study treatment and during the course of the study (refer to Appendix 4).
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing with study treatment and for the following duration after discontinuation of study treatment:
    - For patients enrolled in FGF401 single agent: 3 days after the last dose of FGF401
    - For patients enrolled in FGF401 in combination with PDR001: 150 days after the last dose of PDR001, and 3 days after the last dose of FGF401 in cases where PDR001 was discontinued more than 150 days before the last dose of FGF401

    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

      In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate [generally age from 40 to 59 years], history of vasomotor symptoms [e.g. hot flush]) in the absence of other medical justification, or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
16. Sexually active males unless they use a condom during intercourse while receiving study treatment and for the following period after the last dose of study treatment, and should not father a child in this period.
    - For patients enrolled in FGF401 single agent: 3 days after the last dose of FGF401

[redacted]

- For patients enrolled in FGF401 in combination with PDR001: 150 days after the last dose of PDR001, and 3 days after the last dose of FGF401 in cases where PDR001 was discontinued more than 150 days before the last dose of FGF401

A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

17. Major surgery within 2 weeks of receiving the first dose of study treatment (mediastinoscopy, insertion of a central venous access device and insertion of a feeding tube are not considered major surgery).

In addition patients eligible for the **FGF401 in combination with PDR001** part must not meet **any** of the below criteria:

18. Clinically significant pleural effusion that either required tapping or is associated with shortness of breath.
19. Known human immunodeficiency virus (HIV) infection or known acquired immunodeficiency syndrome.
20. Active HBV or HCV infection. Patients whose disease is controlled under antiviral therapy can be included.
21. Active known or suspected autoimmune disease. Patients with vitiligo, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger can be included. Patients previously exposed to anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or with replacement therapy for endocrinopathies can be included.
22. History of severe hypersensitivity reactions to any ingredient of study treatment and other mAbs and/or their excipients
23. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
    - Clinically significant or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2), uncontrolled hypertension (defined by Systolic Blood Pressure > 160 mmHg/ Diastolic Blood Pressure > 100mmHg (average of three consecutive readings) at rest despite medical treatment, clinically significant arrhythmia
    - QTcF > 470 msec on screening ECG (as mean of triplicate ECGs) or congenital long QT syndrome
    - Acute myocardial infarction or unstable angina pectoris < 3 months prior to screening
24. Use of systemic chronic steroid therapy (≥ 10mg/day prednisone or equivalent) or any immunosuppressive therapy two weeks prior to start of study treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed.
25. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment (except inactivated seasonal influenza vaccines).
26. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents ≤ 2 weeks prior to start of study treatment. If erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained.
27. History of liver or other organ transplantation.

[redacted]

28. History of immunotherapy-induced pneumonitis or current pneumonitis grade > 2.
29. Patients who discontinued prior anti-PD-1/PD-L1 therapy due to an anti PD-1/PD-L1-related toxicity.

6 Treatment

6.1 Study treatment

The study treatments are FGF401 as single agent or FGF401 in combination with PDR001. There is no reference therapy.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study drugs	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
FGF401	capsule for oral use	as assigned	once daily (QD) on a continuous schedule
PDR001	intravenous infusion	300mg	every three weeks (3QW)

Patients will be assigned to receive FGF401 on a continuous once daily dosing regimen or the combination of FGF401 on a continuous once daily dosing regimen and PDR001 administered every three weeks.

The FGF401 dose regimen may change from QD to BID at any time during the study (Section 4.1).

FGF401

FGF401 will be administered orally on a flat scale of mg/day and not by weight or BSA.

FGF401 should be taken as follows:

- Patients should be instructed to take their dose at approximately the same time every day.
- On days when blood for PK samples need to be collected prior to taking study drug, patients should be instructed to bring their drug supply to the site, and take the dose in the clinic, under supervision of the site personnel.
- Each dose should be taken with a glass of water and consumed over as short a time as possible unless otherwise instructed.
- Patients should be instructed to swallow pill(s) whole and to not chew or open them.
- FGF401 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal (unless otherwise instructed). Water and other medications are permitted during this period.
- On days of PK/[redacted] sampling, every effort must be made to capture the time of any vomiting within 4 hours of drug administration in both source documents and corresponding eCRF. The occurrence and frequency of any vomiting and/or diarrhea (or

[redacted]

increase stool frequency) during a treatment cycle must be noted in the Adverse Events eCRF.

- If vomiting occurs during the course of the treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- If the patient forgets to take his/her daily dose, then he/she should take FGF401 within 6 hours after the missed dose. If more than 6 hours have passed, then that dose should be omitted and the patient should continue treatment with the next scheduled dose.
- Patients should inform the investigational site staff of any missed or delayed doses.

Exploratory food effect cohort- FGF401 single agent

- Patients will be treated under fed conditions only when he/she is allocated to the food effect cohort in the phase I part.
- Patients enrolled in the food effect cohorts will receive each dose of FGF401 with a light meal. FGF401 needs to be administered within 30 minutes following the assigned meal, see Appendix 8 for test meal guidance.
- On days of PK profiles collection (Section 7.2.3.1), the light breakfast will be adapted to the local preference and prepared by a registered dietician.

PDR001

PDR001 will be administered via intravenous infusion once every 3 weeks (Section 6.6).

Sequence of FGF401 and PDR001 administration

FGF401 will be administered prior to PDR001 along with PDR001 pre-medication (if pre-medication is necessary). The sequence will allow consistent time of daily dosing for FGF401. A minimum of 1 hour must pass from the time of FGF401 dose administration to the administration of PDR001.

6.1.2 Ancillary treatments

6.1.2.1 Infusion reactions with PDR001

Patients should not receive pre-medication to prevent an infusion reaction before the first infusion of study treatment, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will discontinue study treatment. The patient may resume study treatment following documented discussion with the Novartis medical monitor. Guidelines on management of infusion reactions are provided in Table 6-5.

The CTCAE category of "Infusion related reaction" should be used to describe study treatment related infusion reactions, unless the investigator considers another category, such as "Allergic

[redacted]

reaction," "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

6.1.3 Treatment duration

Patients may continue study treatment until they experience any of the following:

- Disease progression (radiologically documented according to RECIST v1.1) as assessed by the Investigator if they are treated with FGF401 single agent
- Disease progression per irRC if they are treated with FGF401 in combination with PDR001. These patients should not be withdrawn from study treatment due solely to progressive disease per RECIST v1.1. Refer to Section 7.1.3 and Section 7.1.4 for further details.
- Unacceptable toxicity
- Treatment is discontinued at the discretion of the Investigator or the patient

Patients who permanently discontinue the study treatment for any reason other than disease progression or withdrawal of consent shall continue efficacy assessments as scheduled in the protocol Section 7.1.5 until the time of disease progression.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

The recommended starting dose of FGF401 single agent for patients enrolled in this trial is 50 mg p.o. administered continuously once daily (see Appendix 7). This dose is expected to be safe and might be pharmacologically active based on human efficacious dose prediction. Safety of the starting dose is supported by results of 4-week Good Laboratory Practice (GLP) toxicology studies conducted in mice and dogs [redacted]

[redacted]

The starting dose of FGF401 in combination with PDR001 is 80mg QD (fasted) which is one dose level below the declared RP2D for FGF401 as single agent. The RP2D for FGF401 as single agent is 120mg QD administered under fasted conditions.

PDR001 will be administered at a fixed dose of 300mg i.v. every three weeks which is the RP2D declared for PDR001 as single agent.

The starting dose of the FGF401 in combination with PDR001 selected satisfies the EWOC criteria (Section 2.3) for the combination BLRM.

6.2.2 Provisional dose levels

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial for FGF401 single agent and in combination with PDR001. Dose escalation will continue until MTD is reached and/or RP2D is determined. At all decision time points, the BLRM permits alterations in the dose increments based on the observed DLTs.

If at any time during the phase I of the FGF401 single agent part of the study, the pre-clinical and/or clinical data suggest change of dosing schedule, such as BID dosing or intermittent dosing, then the starting total daily dose will be a dose that has previously been confirmed to be well tolerated on a continuous once daily dosing schedule within this study and is supported by an adjusted BLRM (see Section 6.2.3.1 and Section 10.4 for details).

With the exception of starting dose level 1, actual dose levels will be determined following a discussion with the participating Investigators during the dose escalation teleconferences.

The dose for PDR001 will be fixed for all dose escalation cohorts in the FGF401 and PDR001 combination part of the study (Section 6.2.1).

Table 6-2 FGF401 Provisional dose levels

Dose level	Proposed total daily dose*	Increment from previous dose
FGF401 as single agent		
-2**	20 mg	-33.3%
-1**	30 mg	-40%
1	50 mg	(starting dose)
2	100 mg	100%
3	200 mg	100%
4	250 mg	25%
5	300 mg	20%
6	400 mg	33%
7	500 mg	25%

[redacted]

Dose level	Proposed total daily dose*	Increment from previous dose
FGF401 in combination with PDR001		
-1	50mg	-37.5%
1	80 mg	starting dose
2	120mg	50%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Dose levels may also be skipped if the safety data and BLRM analyses support a higher increase limited to at most 100% increase in dose level (e.g. a dose increase from 100 mg to 200 mg with the same frequency). Cohorts may be added at any dose level below the MTD/RP2D in order to better understand safety, PK [redacted]
**Dose level -1 and -2 represent treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -2 is permitted for this study.

6.2.3 Guidelines for dose escalation and determination of MTD

6.2.3.1 MTD definition

The MTD is defined as the highest drug dosage not expected to cause DLT in 33% or more of the treated patients in the evaluation period of FGF401 single agent and FGF401 in combination with PDR001 during the phase I respective parts of the study. The evaluation period of DLTs for the dose escalation decisions is defined as 1 cycle (21 days) from treatment start for FGF401 single agent and as 2 cycles (42 days) starting from the first dose of PDR001 administered in combination with FGF401. Adverse events and laboratory abnormalities considered to be DLTs are defined in Table 6-3.

6.2.3.2 Dose cohort modification

For the purposes of dose escalation decisions, each cohort will consist of 1 to 6 newly enrolled evaluable patients for the FGF401 single agent and, 3 to 6 newly enrolled evaluable patients for the FGF401 in combination with PDR001, who will be treated at the specified dose level. The first cohort will be treated with the starting dose as described in Section 6.2.1. For the FGF401 and PDR001 combination, for each untested dose level the administration of the first dose of the study treatment will be staggered by 24 hours for the first three patients. When two patients enrolled in an escalation arm (FGF401 single agent or in combination with PDR001; who may be in different cohorts) have experienced a toxicity of CTCAE grade 2 for which relationship to study drug cannot be ruled out; or when any single patient experiences a DLT or AE of CTCAE grade 3 or greater during Cycle 1, the cohort size will be changed to between 3 and 6 evaluable patients for the current and subsequent cohorts.

Patients must complete a minimum of 1 cycle of treatment with FGF401 single agent and a minimum of 2 cycles of treatment with FGF401 in combination with PDR001, with the minimum safety evaluation and drug exposure or have had a DLT within the evaluation period to be considered evaluable for dose escalation decisions (Section 10.1.4). Dose escalation decisions will occur when the cohort of patients has met these criteria.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during the DLT evaluation period, PK [redacted] data from evaluable patients. The recommended dose for the next cohort of patients will be guided by the Bayesian models with [redacted]

EWOC principle (Section 2.2). The adaptive Bayesian methodology provides an estimate of all dose levels of FGF401 single agent and FGF401 in combination with PDR001 that do not exceed the MTD for each treatment and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose and/or changes of dosing schedule may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data. Any dose escalation decisions made by Investigators and Novartis personnel will not exceed the dose level recommended by the Bayesian model using the EWOC principle. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If 2 patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the Bayesian model will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level that satisfies the EWOC criteria. However, if 2 patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 patients are treated on this dose level with 2 DLT observed), further enrollment to that cohort will stop, the Bayesian model will be updated with this new information and re-evaluation of the available safety, PK, [redacted] data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose cohort only if the dose still meets the EWOC criteria and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose as agreed by Investigators and Novartis personnel and if the Bayesian model predicts that the risk for this lower dose to exceed the MTD remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC criteria are satisfied) and Investigators and Novartis personnel agree.

Dose escalation will continue until identification of the MTD or a suitable lower dose for expansion. This will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
    a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
    b. a minimum of 21 patients for the FGF401 single agent and a minimum of 12 patients for the FGF401 in combination with PDR001 have already been treated on the trial, or
    c. significant activity is seen early in the phase I part, in which case a recommended dose for expansion may be made and the phase II Groups may be initiated without determination of the MTD
3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference.

To better understand the safety, tolerability and PK of FGF401 as single agent and in combination with PDR001, additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

[redacted]

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the Bayesian model will be updated with this new information before any additional patients are enrolled at that higher dose level. Patients ongoing will continue treatment at their assigned dose levels.

In the event of a change in dosing schedule for either FGF401 single agent or FGF401 in combination with PDR001, then a new Bayesian model will be set up. This new Bayesian model will have the same functional form as that described in Section 10.4.2.1 (for FGF401 single agent) and in Section 10.4.2.2 (for FGF401 in combination with PDR001) and will incorporate existing dose escalation data in the prior distributions and a starting dose will be identified at that time. Subsequent dosing decisions for the new schedule will follow the same rules defined within the above paragraphs of this section.

6.2.3.3 Implementation of dose escalation decisions

To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the Bayesian model, and the available PK [redacted] information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.4 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After the fourth cycle is completed, individual patients may be considered for treatment at a dose of FGF401 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of FGF401, he or she must have tolerated the lower dose for at least four cycles of therapy without experiencing any treatment -related toxicity defined as CTCAE grade ≥ 2 or worse than baseline at the lower dose originally assigned. Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and has not exceeded the maximum tolerated dose (MTD).

There is no limit to the number of times a patient may have his or her dose of FGF401 increased. For any further increase after the initial intra-patient dose escalation, the same rules as for the initial intra-patient dose escalation will apply.

Consultation and agreement with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF. Data from the DLT evaluation period at the new dose level will not be formally included into the statistical model describing the relationship between dose and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation teleconference.

6.2.4 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the evaluation period of DLTs and meets any of the criteria included in Table 6-3. For the purpose of dose-escalation decisions, DLTs will be considered and included in the Bayesian model. However, events occurring after the DLT evaluation period may contribute to the determination of the RP2D. DLTs will not be collected during the phase II dose expansion parts of the study.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

Table 6-3 Criteria for defining dose-limiting toxicities

Toxicity	Any of the following criteria occurring in the evaluation period during the phase I part of the study for which relationship to study treatment cannot be ruled out [a]
Hematology	Any Grade 3 hematologic toxicity, lasting for >7 consecutive days
	Any ≥Grade 4 hematologic toxicity of any duration
	≥Grade 3 Febrile neutropenia
Renal	≥Grade 3 serum Creatinine increased
Pancreas	Grade 3 Lipase or Serum Amylase increased (asymptomatic), which is not resolved to ≤ Grade 2 within 7 days
	Grade 4 Lipase or Serum Amylase increased (asymptomatic) of any duration
	≥Grade 3 Pancreatitis
Cardiac	≥Grade 3 cardiac disorders
	≥Grade 3 ECG QTc corrected interval prolonged
	Any cardiac event that is symptomatic or requiring medical intervention
General disorders	Grade 3 Fatigue, lasting for >7 consecutive days
Gastrointestinal disorders	Grade 2 Diarrhea, which is not resolved to ≤ Grade 1 within 7 days after starting an adequate treatment
	Grade 3 Diarrhea lasting for more than 24 hours after starting an adequate treatment OR improved to Grade 2 within 24 hours but not resolved to ≤ Grade 1 within 7 days after starting an adequate treatment
	≥Grade 4 Diarrhea
	Grade 3 Nausea, lasting for >48 hours, despite the use of adequate treatment
	≥Grade 3 Vomiting, lasting for >24 hours, despite the use of anti-emetic therapy
Hepatic	For patient's baseline bilirubin within normal range: Blood bilirubin increased to > 2.0 x ULN
	For patient's baseline bilirubin out of normal range: Blood bilirubin increased to > 1.5 times above baseline
	For patient's baseline AST or ALT within normal range: AST or ALT increased to > 5.0 x ULN
	For patient's baseline ASTor ALT out of normal range: AST or ALT increased to > 3 times above baseline AND > 5.0 x ULN
Metabolic	Serum Pi > 7.0 mg/dL which is not resolved to ≤ 7.0 mg/dL within 7 days after the maximum dosing of phosphorus lowering therapy

[redacted]

	Serum Pi > 9.0 mg/dL
	≥ Grade 3 hypercalcemia
Other toxicity	Any other CTCAE Grade ≥3 toxicity (**except** those that can be resolved within 7 days and are considered by the investigator to be not clinically important)
	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in the evaluation period, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher.
In addition, the below criteria are considered as DLTs only for the FGF401 and PDR001 combination	
Eye disorders	Grade 2 eye pain or changes in vision that does not respond to topical therapy and does not improve to Grade 1 within 2 weeks of the initiation of topical therapy or requires systemic treatment
Infection	Grade 3 infection or fever in the absence of neutropenia lasting for > 5 consecutive days Grade 4 infection
Pneumonitis	Grade 2 pneumonitis not resolving within 7 days after starting treatment with corticosteroids ≥ Grade 3 pneumonitis
Immune-mediated toxicities	Grade 3 immune mediated toxicities which are not resolved to ≤ Grade 1 within 7 days despite treatment with corticosteroids. Grade 4 immune mediated toxicities
[a] CTCAE version 4.03 will be used for all grading.	

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule due to treatment related toxicities, dose adjustments are permitted in order to allow the patient to continue the study treatment.

Patients in the FGF401 and PDR001 combination, who discontinue treatment due to PDR001 or FGF401 related toxicities may continue treatment with FGF401 or PDR001 single agent respectively, after documented discussion with the Novartis medical monitor.

All changes in the administration of FGF401 or PDR001 must be recorded on the respective Dosage Administration Record eCRF pages.

The following guidelines for FGF401 either administered as single agent or in combination with PDR001 need to be applied:

- For the phase I dose escalation part of the study, dose reductions for FGF401 during the evaluation period of DLTs are only allowed if a DLT is observed and recorded.
- All dose modifications should be based on the worst preceding toxicity and guidelines are provided in Table 6-4.
- If a patient requires a dose interruption of >21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment.
- In exceptional situations, study treatment may continue even if the patient experienced one of the treatment stopping rules. The decision to allow for continuation of treatment will be made on a case-by-case basis following documented discussion between the Novartis medical monitor and the Investigator.

[redacted]

- If a patient remains on study treatment despite dose interruption of > 21 days, i.e. patient with evidence of clinical benefit and in the opinion of the investigator it is in the best interest of the patient to remain on study, then the rationale for remaining on the study and the decision and documentation of the discussion with the Novartis medical monitor must be available in the source documentation and described as an investigator comment in the eCRF.

The following guidelines for PDR001 need to be applied:

- Dose reductions are not permitted for PDR001.
- PDR001 may be delayed due to toxicities. The PDR001 dosing may resume once the adverse event has resolved to ≤ Grade 1 or to the patient's screening value and the start of the cycle will be shifted accordingly. Disease assessments will continue to occur at the frequency that was originally specified within protocol.
- Overall, for adverse events of potential immune-related etiology (irAE) that do not recover to ≤ Grade 1 or patient's screening value at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent within 12 weeks after initiation of immunosuppressive therapy, PDR001 must be permanently discontinued.
- If a patient experiences an AE meeting the criteria for DLT as outlined in Section 6.2.4 (including events occurring after cycle 2), treatment with PDR001 should be withheld. The same applies for any Grade 3 irAE that would require the use of systemic steroids. A decision to resume treatment with PDR001 following the occurrence of a DLT or any Grade 3 irAE is at the discretion of the Investigator.
- If the Investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to Grade 1, or to resume without dose reduction of FGF401 if applicable, this may be permitted on a case by case basis, following documented discussion with the Novartis medical monitor.
- If more than 12 consecutive weeks are required before recovery from PDR001-related toxicities, then the patient must permanently discontinue PDR001 treatment.
- Table 6-4 and Table 6-5 outline the recommended dose modifications for selected toxicities. Additional recommended dose modifications are provided in the Appendix 11, which outlines management algorithms for the following groups of AEs: Pulmonary, Gastrointestinal, Renal, Endocrinopathy, Hepatic and Skin.

[redacted]

Table 6-4 Criteria for interruption and re-initiation of FGF401 as single agent and in combination with PDR001

Recommended Dose Modifications for FGF401 For the FGF401 in combination with PDR001 treatment: Dose level maintenance, dose omission and treatment discontinuation refer to both FGF401 and PDR001. Reduction of one dose level refers to FGF401 only while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade	Recommended dose modifications any time during a cycle of therapy (including intended day of dosing)
No toxicity	Maintain dose level
Investigations (Hematologic)	
Neutropenia (Neutrophil count decreased)	
Grade 3 (ANC < 1000 - 500/mm^3)	Maintain dose level, if not resolved to ≤ Grade 1 or baseline* within 7 days, then omit dose until resolved to ≤ Grade 1 or baseline, and then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3)	Omit dose until resolved to ≤ Grade 1 or baseline, then ↓ 1 dose level
Thrombocytopenia (Platelet count decreased)	
Grade 3 (PLT < 50,000 – 25,000/mm^3)	Maintain dose level, if not resolved to ≤ Grade 1 or baseline within 7 days, then omit dose until resolved to ≤ Grade 1 or baseline, and then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1 or baseline, then ↓ 1 dose level
Grade 3 Febrile neutropenia	Omit dose until resolved, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Investigations (Renal)	
Serum creatinine increased	
Grade 1 (> 1 - 1.5 x baseline; > ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 – 3.0 x baseline; > 1.5 - 3.0 x ULN)	Maintain dose level
Grade 3 (> 3.0 x baseline; > 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ Grade 1 or baseline, then ↓ 1 dose level
Grade 4 (> 6.0 x ULN)	Omit dose and discontinue patient from study drug treatment
Investigations (Pancreatic)	
Asymptomatic Amylase and/or Lipase increased	
Grade 3 (> 2.0 - 5.0 x ULN)	Maintain dose level, if not resolved to ≤ Grade 1 or baseline within 7 days, then omit dose until resolved to ≤ Grade 1 or baseline, and then ↓ 1 dose level
Grade 4 (> 5.0 x ULN)	Omit dose and discontinue patient from study drug treatment

[redacted]

Recommended Dose Modifications for FGF401 For the FGF401 in combination with PDR001 treatment: Dose level maintenance, dose omission and treatment discontinuation refer to both FGF401 and PDR001. Reduction of one dose level refers to FGF401 only while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade	Recommended dose modifications any time during a cycle of therapy (including intended day of dosing)
≥Grade 3 Pancreatitis	Omit dose and discontinue patient from study drug treatment
Investigations (Hepatic)	
Blood bilirubin increased For patient's baseline total bilirubin is ≤ ULN	
> ULN – 2.0 x ULN	Maintain dose level
> 2.0 - 3.0 x ULN	Omit dose and consider excluding immune mediated etiology** until resolved to ≤ 2.0 x ULN, then: If resolved in ≤ 7 days, then ↓ 1 dose level (any subsequent > 2.0 x ULN requiring discussion with Novartis) If resolved in > 7 days, then discontinue patient from study drug treatment
> 3.0 x ULN	Omit dose and discontinue patient from study drug treatment
Blood bilirubin increased For patient's baseline total bilirubin is > ULN	
> ULN – 1.5 times above baseline	Maintain dose level
> 1.5 – 3.0 times above baseline	Omit dose and consider excluding immune mediated etiology** until resolved to ≤ 1.5 times above baseline, then: If resolved in ≤ 7 days, then ↓ 1 dose level (any subsequent > 1.5 times above baseline requiring discussion with Novartis) If resolved in > 7 days, then discontinue patient from study drug treatment
> 3.0 times above baseline	Omit dose and discontinue patient from study drug treatment
AST and/or ALT increased For patient's baseline AST/ALT are ≤ ULN	
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 – 20.0 x ULN)	Omit dose and consider excluding immune mediated etiology** until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then ↓ 1 dose level (any subsequent > 5.0 x ULN requiring discussion with Novartis) If resolved in > 7 days, then discontinue patient from study drug treatment
Grade 4 (> 20.0 x ULN)	Omit dose and discontinue patient from study drug treatment
AST and/or ALT increased For patient's baseline AST/ALT are > ULN	

[redacted]

Recommended Dose Modifications for FGF401 For the FGF401 in combination with PDR001 treatment: Dose level maintenance, dose omission and treatment discontinuation refer to both FGF401 and PDR001. Reduction of one dose level refers to FGF401 only while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade	Recommended dose modifications any time during a cycle of therapy (including intended day of dosing)
> ULN – 3.0 times above baseline	Maintain dose level
> 3.0 – 5.0 times above baseline but < 5.0 x ULN	Maintain dose level
> 3.0 – 5.0 times above baseline AND > 5.0 x ULN	Omit dose and consider excluding immune mediated etiology** until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then ↓ 1 dose level (any subsequent > 5.0 x ULN requiring discussion with Novartis) If resolved in > 7 days, then discontinue patient from study drug treatment
> 5.0 times above baseline	Omit dose and discontinue patient from study drug treatment
Metabolic	
Hyperphosphatemia	Please refer to the guidelines for study drug-induced hyperphosphatemia provided in Appendix 6.
Hypercalcemia	
Grade 1	Maintain dose level
Grade 2	Maintain dose level and start adequate therapy immediately
≥Grade 3	Start adequate therapy immediately and omit dose until resolved to ≤ G1, then: If resolved in ≤ 7 days, then ↓ 1 dose level If resolved in > 7 days, then discontinue patient from study drug treatment
Gastrointestinal disorders	
Diarrhea Grade 1-4	Please refer to the guidelines for FGF401-induced diarrhea provided in Appendix 5. If diarrhea is not improved with cholestyramine, consider immune mediated toxicity and refer to guidelines provided in Appendix 11
Grade 3 Nausea	Maintain dose level, if not resolved to ≤ Grade 2 within 48 hours despite the use of adequate treatment, then omit dose until resolved to ≤ Grade 2, and then ↓ 1 dose level
≥ Grade 3 Vomiting	Maintain dose level, if not resolved to ≤ Grade 2 within 24 hours after the optimal anti-emetic therapy start, then omit dose until resolved to ≤ Grade 2, and then ↓ 1 dose level
General disorders	
Grade 3 Fatigue	Maintain dose level, if not resolved to ≤ Grade 2 within 7 days, then omit dose until resolved to ≤ Grade 2, and then ↓ 1 dose level
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	**Permanently discontinue study treatment.**
Other adverse events	

[redacted]

Recommended Dose Modifications for FGF401 For the FGF401 in combination with PDR001 treatment: Dose level maintenance, dose omission and treatment discontinuation refer to both FGF401 and PDR001. Reduction of one dose level refers to FGF401 only while PDR001 dose level should be maintained, unless otherwise specified.	
Worst toxicity CTCAE v4.03 Grade	Recommended dose modifications any time during a cycle of therapy (including intended day of dosing)
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level. Note: Dose level can be maintained in case they are resolved within 7 days and are considered not clinically important.
Grade 4	Omit dose and discontinue patient from study
All dose modifications should be based on the worst preceding toxicity. CTCAE version 4.03 will be used for all grading. *baseline refers to respective laboratory values before start of the study treatment ** in case immune mediated etiology cannot be excluded; consider following the guidelines in Appendix 11	

[redacted]

Table 6-5 Criteria for interruption and re-initiation of PDR001 treatment

Recommended dose modifications for PDR001	
Worst toxicity CTCAE v4.03 grade	Anytime during a cycle of therapy and after the DLT evaluation period*
Infusion Reaction	
Grade 1	Infusion interruption not indicated; decrease infusion rate until recovery of symptoms
Grade 2	Stop infusion of PDR001. Before resuming infusion pre-medicate according to local institutional guidelines. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue patient from PDR001
Grade 3 or 4	Discontinue infusion immediately, and discontinue patient from PDR001
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue study treatment
Pulmonary: Pneumonitis	Management Algorithms (Appendix 11)
Renal: Serum Creatinine	Management Algorithms (Appendix 11)
Gastro-intestinal: Diarrhea/Colitis	Management Algorithms (Appendix 11)
Skin: Rash	Management Algorithms (Appendix 11)
Endocrinopathy: TSH	Management Algorithms (Appendix 11)
Other clinically significant toxicities thought to be immune-mediated and not covered in Appendix 11	
Grade 1	Monitor closely until resolution and treat symptoms as appropriate
Grade 2	Delay PDR001 treatment until resolved to ≤ Grade 1
Grade 3 or 4	Permanently discontinue PDR001 treatment
Cytokine Release Syndrome (CRS)	
Grade 2, 3 or 4	If CRS is suspected (very high fever and precipitous drops in blood pressure) treat with corticosteroids. Take blood for cytokine measurements immediately after the occurrence and during treatment (Section 7.2.2.5.10). Following approval of protocol amendment 05, no further sample collection will be performed for the cytokine measurements. If very high levels of IL-6 can be confirmed, a more specific treatment may be used.
*for infusion reaction and cytokine release syndrome the dose modifications are applicable anytime during a cycle of therapy (including intended day of dosing)	

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) until resolution or stabilization of the event, whichever comes first. For patients with ≥ Grade 2 hepatic toxicities which relationship to study treatment cannot be ruled out, the hepatic laboratory parameters should be followed up within 72 hours.

The emergence of irAE may be anticipated based on general experience in clinical studies with similar class of compounds that block the negative immune regulators.

[redacted]

An irAE is any clinically significant adverse event affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE. Management Algorithms (Appendix 11) have been developed to assist Investigators in assessing and managing specific groups of AEs.

All patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-weeks intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

In case of toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 7.2.2.5.10 must be performed. Following approval of protocol amendment 05, no further sample collection will be performed for the cytokine analysis.

All patients must be followed-up for irAEs, AEs and SAEs as described in Section 7.1.6.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Prophylactic or supportive treatment for expected toxicities, including management of study-treatment induced adverse events will be as per institutional guidelines. Recommended guidelines for the management of FGF401-induced diarrhea and hyperphosphatemia are provided in Appendix 5 and Appendix 6 respectively. Moreover, patients will not initially receive prophylactic treatment with anti-emetics in cycle 1, but should receive treatment for nausea/vomiting as per institutional guidelines.

In addition, recommended guidelines for prophylactic or supportive treatment for expected toxicities with the FGF401 and PDR001 combination, including management of immune related toxicities, are provided in Section 6.3 and Appendix 11.

Refer to Section 1.2 [redacted]

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. phosphate lowering therapy and anti-diarrhea therapies) and safety of the patient are allowed, except for those prohibited as stated in Section 6.4.3.

Prophylactic phosphate lowering and/or anti-diarrhea therapies should be considered as per the management guidelines provided in Appendix 5 and Appendix 6. Prophylactic phosphate lowering and/or anti-diarrhea therapies are also recommended once the MTD and/or RP2D have

[redacted]

been established during the FGF401 single agent phase I and dose-related hyperphosphatemia and diarrhea have been well-characterized.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior and Concomitant Medications eCRF or the Surgical and Medical Procedures eCRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Medications that are inducers or inhibitors of CYP3A4/5 are not prohibited but should be administered with caution. Concomitant medications that may potentially inhibit BSEP (the known BSEP inhibitors are prohibited), MRP2/3/4, NTCP and OATP1B1/3, which are involved in bile acid transport, should be administered with caution, as increase in bile acid synthesis is expected at efficacious doses. Refer to Appendix 4 for a list of the medications that require caution when concomitantly used with FGF401 as single agent or in combination with PDR001.

Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with PDR001 for patients receiving the FGF401 and PDR001 combination treatment.

6.4.3 Prohibited concomitant therapy

FGF401 is a time-dependent inhibitor of CYP1A2, CYP2C9 and CYP3A4/5. CYP1A2, CYP2C9 and CYP3A4/5 substrates with a narrow therapeutic index (NTI) are prohibited during the course of the study. FGF401 treatment may increase the levels of bile acids as a result of mechanism of action. Therefore medications that are reported to be inhibitors of the bile acid efflux transporter BSEP shall be prohibited during this study.

Additionally, for patients receiving FGF401 in combination with PDR001:

Treatment with the following agents is not permitted within 2 weeks prior to the first dose of study treatment:

- hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF)
- thrombopoietin mimetics or
- erythroid stimulating agents; however, if erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained.

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, for prophylaxis against imaging contrast dye allergy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as chronic obstructive pulmonary disease (COPD) requiring treatment for ≤ 3 weeks. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the

[redacted]

next study drug administration. If more than 10 mg/day prednisone is used, study treatment should be suspended. Topical, inhaled, nasal and ophthalmic steroids are allowed.

The use of live vaccines is not allowed through the duration of the study. Inactivated vaccines are allowed.

During the course of the study, patients must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer or modulate the immune responses. However, limited-field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy after documented discussion with Novartis. Such local therapies administered during the study treatment must be entered into the CRF. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study unless given for the management of immune toxicity.

Refer to Appendix 4 for a list of the medications that are prohibited when concomitantly used with FGF401 as single agent and in combination with PDR001.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for molecular pre-screening or screening as applicable and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No. as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

6.5.2 Treatment assignment

This is a non-randomized trial and Integrated Response Technology (IRT) will not be used. The assignment of a patient to a particular cohort during the phase I parts, and during the phase II parts will be coordinated by Novartis.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take FGF401 as per protocol. FGF401 will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

PDR001 [redacted] will be administered intravenously as a 30 minute infusion (up to 2 hour, if clinically indicated). Further instructions for the preparation and dispensation of PDR001 are described in the Pharmacy Manual.

6.6.1 Study drug packaging and labeling

The FGF401 packaging has a 2-part label. Responsible site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel

[redacted]

will detach the outer part of the label from the packaging and affix it to the source document for that patient's unique subject number.

[redacted]

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and but no information about the patient.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, FGF401 and PDR001 should be stored according to the instructions specified on the drug labels [redacted]

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the drug accountability record. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log according to local institutional drug accountability processes. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

Arrange for drug supply to be destroyed at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. No CRF will be used as a source document. The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

For Japan only, patients are required to be hospitalized in Cycle 1 of the dose escalation parts.

For all visits, there is a ± 3 days window on assessments if not explicitly specified otherwise. In particular, full PK sampling should be performed on the specified day of dosing and time-point. In any case, if the dosing schedule is changed, the visit evaluation schedule will follow Table 7-1 without changes. In general, where possible, every effort must be made to follow the schedule outlined in Table 7-1.

Screening assessments need to be performed within 14 days from the first dose of study treatment with the exception of pregnancy test which must be performed within 72 hours from study treatment start. Laboratory assessments performed as part of the screening evaluations and within 72 hours of the cycle 1 day 1, are not required to be repeated on the first dosing day. . Screening radiological assessment should be performed preferably within 7 days prior to the first study treatment dose; however radiological assessments that are performed up to 21 days before the first study treatment dose will be acceptable; (except whole body scans, if applicable, which can be performed within 6 weeks of study treatment start) On-study radiological assessments can be performed within a ± 7 days window from the scheduled date of the assessment.

Following approval of protocol amendment 05, the ongoing patients will follow a reduced schedule of safety and efficacy assessments as detailed in Table 7-1b. The assessments in Table 7-1 will no longer be applicable. Table 7-1b indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

Other assessments may be performed at the Investigator's discretion following standard of care at the site. When abnormal laboratory values or test results constitute an adverse event, they must be recorded on the Adverse Events eCRF.

[redacted]

Table 7-1 Visit evaluation schedule (applicable for protocol amendment 04 - following approval of protocol amendment 05 refer to Table 7-1b below)

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1					Cycle 2				Subsequent Cycle		End of study treatment	30 or 150-day Safety-FU[a]	Disease progression	Survival FU
Visit Name				Day -14 to Day 1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15				
Obtain molecular pre-screening Informed Consent	D	7.1.1	X as appicable																
Obtain Informed Consent	D	7.1.2		X															
Patient History																			
Demography	D	7.1.2.2	X	X															
Inclusion/exclusion criteria	D	5	X	X															
Relevant medical history/current medical conditions	D	7.1.2.2		X															
Diagnosis and extent of cancer	D	7.1.2.2		X															
Child-Pugh and BCLC classification, applicable to HCC patients	D	7.1.2.2		X															
Prior antineoplastic therapies	D	7.1.2.2		X															

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1					Cycle 2				Subsequent Cycle		End of study treatment	30 or 150-day Safety-FU[a]	Disease progression	Survival FU
Visit Name				Day -14 to Day 1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15				
Prior/concomitant medications	D	7.1.2.2		X	Continuous (for 150-day safety FU: until the 30-day safety FU or the start of new antineoplastic therapy, whatever occurs first)														
Physical examination	S	7.2.2.1		X	X					X				X		X			
Vital signs	D	7.2.2.2		X	X		X		X	X		X	X	X		X			
Height	D	7.2.2.3		X															
Weight	D	7.2.2.3		X	X					X				X		X			
ECOG Performance status	D	7.2.2.4		X	X					X				X		X			
Laboratory assessments																			
Hematology	D	7.2.2.5.1		X	X		X		X	X		X	X	X	X C3/C4 only	X			
Chemistry	D	7.2.2.5.2		X	X		X		X	X		X	X	X	X C3/C4 only	X			
Coagulation	D	7.2.2.5.3		X	X		X			X				X		X			
Urinalysis	D	7.2.2.5.4		X	X											X			
Pregnancy test	D	7.2.2.5.8		X						X				X		X			
	S																X[b]		
[redacted]																			

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1					Cycle 2				Subsequent Cycle		End of study treatment	30 or 150-day Safety-FU[a]	Disease progression	Survival FU
Visit Name				Day -14 to Day 1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15				
AFP, applicable to HCC patients, every 6 weeks	D	7.2.2.5.5			X									X					
Hepatitis markers, every 6 weeks starting from C3	D	7.2.2.5.6		X										X		X			
HIV (for FGF401+PDR001 only)	D	7.2.2.5.6		X															
Thyroid function (for FGF401+PDR001 only)	D	7.2.2.5		X	X					X				X		X			
Cytokines for safety (FGF401+PDR001 only)	D	7.2.2.5.10		X	any time when a suspected cytokine release syndrome occurs, within 5 hours (or as soon as possible) after the occurrence of the AE, and one week after occurrence of the AE														
Efficacy assessments																			
Tumor response assessment , every 6 weeks starting by C3D1	D	7.2.1		X										X		X		X	
Cardiac assessments																			
12-lead ECG	D	7.2.2.6.1		X	X					X				X		X			
PK sampling																			
FGF401 PK sampling (Phase I parts)- all patients	D	7.2.3.1			X	X	X	X	X	X	X			X C3/C4 only					

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1					Cycle 2				Subsequent Cycle		End of study treatment	30 or 150-day Safety-FU[a]	Disease progression	Survival FU
Visit Name				Day -14 to Day 1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15				
FGF401 PK sampling (Phase II parts)- all patients	D	7.2.3.1			X	X	X		X	X	X			X C3-C6 only					
PDR001 PK sampling (Phase I part)- for FGF401+PDR001 only	D	7.2.3.1			X		X		X	X				X up to C6	X for C3 only	X	X[c]		
PDR001 PK sampling (Phase II part)-for FGF401+PDR001 only	D	7.2.3.1			X					X				X up to C6		X	X[c]		
PDR001 immunogenicity (IG) sampling- for FGF401+PDR001 only	D	7.2.3.1			X					X				X up to C6		X	X[c]		
[redacted]																			

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1					Cycle 2				Subsequent Cycle		End of study treatment	30 or 150-day Safety-FU[a]	Disease progression	Survival FU
Visit Name				Day -14 to Day 1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15				
[redacted]																			
[redacted]																			

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1					Cycle 2				Subsequent Cycle		End of study treatment	30 or 150-day Safety-FU[a]	Disease progression	Survival FU
Visit Name				Day -14 to Day 1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15				
FGF401administration	D	6			Continuous														
PDR001 infusion (for FGF401+PDR001 only)	D	6			i.v. every 3 weeks (in case of sequential schedule start from C3D1)														
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5														X	X	X	
Adverse events	D	8	SAE Only	Continuous (for 150-day safety FU: after initiation of new antineoplastic therapy only AEs/SAEs suspected to be related to study treatment will be collected)															
Survival contact	D	7.1.5																	X

[a] for FGF401 single agent safety evaluations for 30 days after the last dose of FGF401. For FGF401 and PDR001 combination safety evaluations for 150 days after the last dose of PDR001 with contacts at 30-, 90- and 150-day (see Section 7.1.6).

[b] only for FGF401 and PDR001 combination with tests every month until the end of 150-day safety FU. Pregnancy tests can be performed at home or at a local doctor's office if the patient is not coming to the clinic.

[c] only for patients coming to the site for the 150-day safety follow-up visit

[redacted]

[e] collect at screening or anytime thereafter

[redacted]

Table 7-1b Visit evaluation schedule – applicable upon approval of protocol amendment 05

	Category	Treatment Phase- all cycles until end of study treatment		End of study treatment	30 or 150-day Safety -FU[a]	Disease progression FU	Survival FU
		FGF401 single agent: Visit every 2 cycles (i.e. every 6 weeks)	FGF401+PDR001 combination: Visit every cycle (i.e. every 3 weeks)				
Visit Name		**Day 1**					
Physical examination	S	X	X	X			
Vital signs	D		X				
Hematology	D	X	X	X			
Chemistry	D	X	X	X			
Pregnancy test	D	X[c]	X	X			
	S				X[b]		
Hepatitis markers	D	X	X every 6 weeks	X			
Tumor response assessment	D	X every 12 weeks		X		X	
FGF401 administration	D	Continuous					
PDR001 infusion	D		X i.v. every 3 weeks				
Adverse events	D	Continuous [a]					
Concomitant medications	D	Continuous [a]					
Antineoplastic therapies since discontinuation of study treatment	D			X	X	X	
Survival contact	D						X

[a] for FGF401 single agent safety evaluations for 30 days after the last dose of FGF401. For FGF401 and PDR001 combination safety evaluations for 150 days after the last dose of PDR001 with contacts at 30-, 90- and 150-day (see Section 7.1.6).

For the 150-day safety FU: After initiation of new antineoplastic therapy only AEs/SAEs suspected to be related to study treatment will be collected. Collection of concomitant medications will be until the 30-day safety FU or the start of new antineoplastic therapy, whatever occurs first.

[b] only for FGF401 and PDR001 combination with tests every month until the end of 150-day safety FU. Pregnancy tests can be performed at home or at a local doctor's office if the patient is not coming to the clinic.

[c] Serum pregnancy test at Day 1 of each cycle (note that on the release date of protocol amendment 05, there were no female participants that are of child-bearing potential on study).

[redacted]

7.1.1 Molecular pre-screening

During the phase I part of FGF401 single agent, FGFR4 and KLB expression will be assessed using RT-PCR and/or IHC assays. Biomarker positivity will be defined by a Novartis designated laboratory that is certified to perform clinical assays. FGF19 mRNA expression will be also assessed by RT-PCR, but it will not be used as inclusion criterion. During the phase II part of the FGF401 single agent, evidence of positive expression of FGFR4 and KLB is required in order to begin screening activities only for patients in Group 3. FGF19 expression will be also assessed, but it will not be used as inclusion criterion. In exceptional cases, patients with a tumor harboring a documented FGFR4 mutation can be enrolled in the study following discussion and agreement with Novartis.

Molecular pre-screening will not be performed for the FGF401 and PDR001 combination part. However, should, the Stage 2 of the FGF401 and PDR001 combination part proceed, based on the interim analyses results (Section 4.2), the FGF pathway expression level and/or FGF19 pathway activation as deemed necessary, will be required for enrollment and molecular pre-screening will be initiated at that stage.

The molecular status must be obtained through the submission of newly obtained tumor samples which are collected after the latest anti-neoplastic treatment failure to a Novartis designated laboratory for testing. The potential patients will be asked to sign a "molecular pre-screening informed consent" to allow for the collection and analysis of the newly obtained tumor samples.

The newly obtained tumor samples can be submitted for analysis as formalin fixed tumor sample or FFPE block prepared from multiple (3-6) passes of a core needle tumor biopsy. For details of sample quality requirements refer to the applicable study Laboratory Manual . If the patient is enrolled in the main study, the newly obtained tumor sample submitted for molecular pre-screening can be used for other [redacted] study assessments. For other details, refer to Section 7.2.4.

7.1.2 Screening

The allocation of patients to treatment cohorts and Groups will be handled by Novartis study team.

A written informed consent form (ICF) will be obtained from each patient before any study related procedures are initiated. Laboratory and radiological evaluations which are part of the patient's standard of care may be performed before obtaining the ICF, if within the acceptable screening window (Section 7.1).

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. A complete list of screening evaluations is provided in the visit of assessments table (Table 7-1).

7.1.2.1 Information to be collected on screening failures

Patients who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as patients who are found not eligible after signing the main study consent will be considered screening failures, and data will be handled in the same manner. The reason

[redacted]

for molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported.

7.1.2.2 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, gender, race) and other background or relevant medical history, including history of disease and current disease status, diagnosis and extent of cancer (for HCC patients, BCLC staging and Child-Pugh classification systems are applied), prior anticancer therapies, prior medication/ significant non-drug therapies and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

7.1.3 Treatment period

A treatment cycle is defined as 21 days (3 calendar weeks) for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 or Table 7-1b following approval of protocol amendment 05 for details of the timing of required assessments and Section 7.1 for visit windows.

Patients may continue treatment with FGF401 single agent or in combination with PDR001 until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient request.

In general, patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue receiving study treatment. In addition, study treatment may be temporarily interrupted to permit local therapy for symptomatic metastases after disease progression has been documented. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator. All patients will continue to follow the assessments as outlined in the visit evaluation table, Table 7-1 or Table 7-1b following approval of protocol amendment 05.

For patients treated with immunotherapy, including PD-1 inhibitor, clinical experience indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing (“mixed response”) (Wolchok 2009). It is therefore reasonable to allow for these possibilities and continue to treat the patient until progression is confirmed and found to be advancing at the next imaging assessment as per irRC. An outline of the irRC is provided in Appendix 9.

Patients treated with FGF401 in combination with PDR001 **will continue study treatment** in additional cycles if they meet the following criteria:

- Unconfirmed irPD, SD/irSD, PR/irPR and unconfirmed CR/irCR.

[redacted]

Patients treated with FGF401 in combination with PDR001 will **not** continue study treatment in additional cycles if they meet any of the following criteria:

- Experience unacceptable toxicity.
- Confirmed irPD. These patients will then enter the Safety follow-up period.
- Patients with an unconfirmed irPD who show signs of clinical deterioration or toxicity will enter the Safety follow-up period, and will continue to be followed-up until confirmed irPD or initiation of a new treatment.

Patients with confirmed irPD might continue receiving study treatment, if the Investigator considers it to be in the patient's best interest to remain on the study, and after documented discussion with the Novartis medical monitor.

These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment. Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care.

7.1.4 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

Study treatment must be discontinued under the following circumstances:

- Adverse events, that results in a significant risk to the patient's safety.
- The following deviation from the prescribed dose regimen for study treatment: dose interruption of > 21 days from the intended day of the next scheduled dose for FGF401 or in case > 12 consecutive weeks are required before recovery from PDR001-related toxicities, unless otherwise specified in Section 6.3.1
- Pregnancy
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-1 or Table 7-1b following approval of protocol amendment 05 (end of study treatment visit) and then enter the follow-up epoch. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.6. An EOT visit should be conducted within 14 days of the last dose of study treatment or within 14 days of the decision to permanently discontinue study treatment. If the patient discontinues from the study treatment at a scheduled visit, the EOT assessment can be performed on that day. An End of Treatment Phase Disposition eCRF page should be completed to include the date and reason for discontinuing study treatment

[redacted]

For patients who discontinue study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 6 weeks or every 12 weeks following approval of protocol amendment 05 until documented disease progression, death, lost to follow-up, or withdrawal of consent.

7.1.4.1 Replacement policy

Phase I Part

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS, enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number (1 or 3 for FGF401 single agent or 3 for FGF401 in combination with PDR001) or at most the maximum number (6) of evaluable patients is achieved within the cohort.

Phase II Part

During the phase II part, no replacement will be needed.

7.1.5 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject does not want to participate in the study anymore, and does not allow further collection of personal data.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.6 Follow up period

Safety follow-up

All patients treated with FGF401 single agent must have safety evaluations for 30 days after the last dose of FGF401.

All patients treated with FGF401 and PDR001 combination must have safety evaluations for 150 days after the last dose of PDR001. During the 150-day safety follow-up for PDR001, the patient should be contacted, by telephone call or visit, at least on day 30, 90, and 150. Concomitant medications will be collected until the 30-day safety follow-up has been completed, or the start of a new antineoplastic therapy, whichever occurs first. A PK and immunogenicity sample should be collected at 150 days as described in Section 7.2.3. If the 150-day safety evaluation is conducted by phone, samples do not need to be collected.

In case patients discontinue PDR001 more than 141 days before the last dose of FGF401, then they must have safety evaluations for 30 days after the last dose of FGF401.

Disease progression follow-up

Any patient who has not progressed at the time of discontinuation of study treatment will continue to have tumor assessments performed every 6 weeks or every 12 weeks following approval of protocol amendment 05 until disease progression, initiation of subsequent anticancer therapies, or death, whichever occurs first.

Survival follow-up

Upon completion of the 30 or 150 day safety follow-up as applicable or disease progression follow-up, all patients, except those who died, withdrew consent or were lost to follow-up, will be followed for survival (can be done by telephone call) every 4 weeks (±1 week) until death. Completion of the survival follow-up period will occur once a minimum of 80% of patients in the phase II part for both FGF401 single agent and FGF401 in combination with PDR001 have died, have been lost to follow-up, or have been followed for survival for minimum 18 months after receiving the first dose of study treatment, whichever occurs first.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the Investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient (e.g. dates of telephone calls, e-mail, letters). A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Disposition eCRF page.

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

Following approval of protocol amendment 05, efficacy assessments will be performed every 12 weeks until progression of disease.

Table 7-2 Imaging collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI with contrast enhancement (for HCC patients, the scan must include dual-phase imaging of the entire liver)	Mandated	Mandated, every 6 weeks (±7 days)
Whole body bone scan	If clinical evidence of bone metastasis	If clinically indicated
Brain CT or MRI	If clinical evidence of brain metastasis	If brain lesions at screening every 6 weeks (±7 days)
Bone X-ray, CT or MRI (bone lesions only)	If lesions on bone scan that are not visible on the chest, abdomen or pelvis CT/MRI	If bone lesions at screening, then every 6 weeks (±7 days)
Skin color photography (skin lesions only)	If clinical evidence of skin lesions	If skin lesions at screening, then every 6 weeks (±7 days) If no skin lesion noted at screening, then if clinical indicated

Tumor response will be determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 1) for patients treated with FGF401 single agent. In addition for patients treated with FGF401 and PDR001 combination the tumor response will be determined according to RECIST v1.1 (Appendix 1) and irRC (Appendix 9). The local investigator's assessment will be used for the primary endpoint analysis and for treatment decision making.

Additionally, imaging data from the FGF401 single agent and the FGF401 and PDR001 combination phase II parts of the study will be centrally collected and checked for quality by an imaging CRO designated by Novartis and may undergo independent review according to the Novartis guideline, based on RECIST v1.1 and irRC (as applicable) if deemed necessary. Novartis may also decide to have a central review of the radiological assessments from the dose escalation phase I parts of the study. In such case, the Investigators will be instructed on how to send data from these radiological assessments to a Novartis designated CRO for central review, when needed.

Following approval of protocol amendment 05, the imaging data (CT/MRI scans) will not be centrally collected.

CT/MRI scans will be performed at baseline within 21 days before start of treatment and subsequently every 6 weeks starting on cycle 3 day 1 until progression of disease (Section 7.1.3). There is a ±7 days evaluation window for all tumor assessments, see Table 7-2 for details. CT/MRI scan will be performed at EOT if not conducted within 30 days prior to EOT. Disease progression follow-up should be performed as described in Section 7.1.6.

[redacted]

Imaging evaluations subsequent to an off-schedule confirmatory scan, should be performed according to the original assessment schedule. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

If at baseline a patient has a medical contraindication to CT i.v. contrast or develops a contraindication during the trial, a non-contrast CT of chest plus contrast-enhanced MRI of abdomen is acceptable.

Patients with clinical evidence of bone metastases must have a whole body bone scan at baseline per local institutional practice. Lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen or pelvis CT (or MRI) scan should be imaged at baseline and followed at subsequent scheduled visits using localized CT, MRI or X-ray. After baseline, whole body bone scans need not be repeated, unless clinically indicated.

Skin lesions present at baseline should be documented using color photography, including a ruler, so that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

Baseline brain CT or MRI will be mandated for patients with clinical sign or symptoms of brain metastases. Subsequent brain scans should only be conducted if brain lesions are documented at baseline for eligible patients or in patients that develop symptoms indicative of brain metastases.

All CRs and PRs must be confirmed by a second assessment not earlier than 4 weeks after the criteria for response are first met.

Any potentially measurable lesion that has been previously treated with radiotherapy and/or loco-regional therapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy and/or loco-regional therapy has clearly progressed since these therapies, it can be considered as a measurable lesion.

PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessment as well as collection of all serious and non-serious adverse events. For details on AE collection and reporting, refer to Section 8.

Following approval of protocol amendment 05, assessments for height, weight, and performance status are not required by the protocol.

7.2.2.1 Physical examination

A complete physical examination must be performed as indicated in Table 7-1 or Table 7-1b following approval of protocol amendment 05.

Physical examination will be performed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

[redacted]

Physical examination will be performed according to the standards at each institution. Usually, the physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams should be considered.

Information about the physical examination must be present in source documents at the study site. Significant findings that are present prior to signing of informed consent form for the study must be included in the Medical History eCRF. Significant new findings that begin or worsen after informed consent for the study must be recorded on the Adverse Events eCRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1 or Table 7-1b following approval of protocol amendment 05 according to the standards at each institution.

Vital signs will be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

Following approval of protocol amendment 05, vital signs will be performed only for patients treated with FGF401 and PDR001 combination as indicated in Table 7-1b.

7.2.2.3 Height and weight

Height (screening only) in centimeters and body weight in kilograms (in indoor clothing, without shoes) will be measured as indicated in Table 7-1.

7.2.2.4 Performance status

ECOG performance status will be assessed as defined in Table 7-1 and Table 7-3.

Table 7-3 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

7.2.2.5 Laboratory assessments

The laboratory parameters assessed for safety purposes will be evaluated locally at the site, except for [redacted] cytokines for safety (applicable for the FGF401 in combination with PDR001 only), which will be analyzed centrally at the Novartis designed central laboratory. Refer to Table 7-4 and Table 7-5 or Table 7-4b following approval of protocol amendment 05

[redacted]

for a summary of the parameters to be evaluated according to Table 7-1, or Table 7-1b following approval of protocol amendment 05.

Unscheduled assessment can be performed if clinically indicated.

Table 7-4 Local clinical laboratory parameters collection plan (applicable for protocol amendment 04 - following approval of protocol amendment 05 refer to Table 7-4b below)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils and others)
Chemistry (Fasting)	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, ionized Calcium, Chloride, Creatinine, Creatine kinase, Direct Bilirubin, Glucose, Gamma-glutamyl transpeptidase, Inorganic phosphorus, Magnesium, Potassium, Sodium, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase
Coagulation	Prothrombin time (PT) or International normalized ratio (INR)
Urinalysis	Macroscopic Panel (Dipstick): Bilirubin, Blood, Glucose, Ketones, Leukocytes, pH, Protein, Specific gravity Any clinically significant findings on dipstick will be followed up with a microscopic evaluation.
Hepatitis markers	HBsAg, HBcAb, HBsAb, HBV-DNA, HCV RNA-PCR
Pregnancy	Serum hCG/urine pregnancy test
HCC patients specific laboratory parameter	
Other	Alpha-fetoprotein
Thyroid function*	Free T4 and TSH (Thyroid Stimulating Hormone)
Virology*	HIV
*applicable only for FGF401 in combination with PDR001	

Table 7-4b Local clinical laboratory parameters collection plan- applicable upon approval of protocol amendment 05

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells
Chemistry (Fasting)	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium, Creatinine, Inorganic phosphorus, Total Bilirubin, Total Cholesterol, Triglycerides
Hepatitis markers	HBsAg, HBcAb, HBsAb, HBV-DNA, HCV RNA-PCR
Pregnancy	Serum hCG/urine pregnancy test

[redacted]

Table 7-5 Central clinical laboratory parameters collection plan**

Test Category	Test Name
[redacted]	[redacted]
Cytokines for safety*	IFN-γ, IL-6
* applicable only for FGF401 in combination with PDR001 ** following approval of protocol amendment 05, [redacted] cytokines for safety are not required	

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-4 or Table 7-4b following approval of protocol amendment 05 will be performed as per the assessment schedule provided in Table 7-1 or Table 7-1b following approval of protocol amendment 05.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-4 or Table 7-4b following approval of protocol amendment 05 will be performed as per the assessment schedule provided in Table 7-1 or Table 7-1b following approval of protocol amendment 05. The patient should be instructed to fast for at least 12 hours before specimen collection.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-4 will be performed as per the assessment schedule provided in Table 7-1.

Following approval of protocol amendment 05, coagulation panel is not required.

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-4 will be performed as per the assessment schedule provided in Table 7-1.

Following approval of protocol amendment 05, urinalysis panel is not required.

7.2.2.5.5 Alpha-fetoprotein

Alpha-fetoprotein will be analyzed for HCC patients on Day 1 of every other cycle from Cycle 1 as per the assessment schedule provided in Table 7-1.

Following approval of protocol amendment 05, alpha-fetoprotein analysis will not be performed.

7.2.2.5.6 Hepatitis markers-Virology

During the screening period, patients must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all patients to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc.), and any past or present HBV symptoms (e.g., jaundice, dark urine, light colored stools, right upper quadrant pain).

Hepatitis B:

At screening, all patients will be tested for:

[redacted]

- HBV-DNA level
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis B surface antibody (HBsAb)

Monitoring for HBV –DNA level on Day 1 of every other cycle from Cycle 3 and EOT is required for:

- Patients known to have a history of HBV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')
- Patients positive for viral load on HBV-DNA test at screening
- Patients positive for any of the serology at screening

Hepatitis C:

All patients will be tested for quantitative HCV RNA-PCR at the screening visit.

Monitoring for HCV RNA-PCR level on Day 1 of every other cycle from Cycle 3 and EOT is required for:

- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')
- Patients positive for viral load on HCV RNA-PCR test at screening

HIV

In addition to the above assessments, for the FGF401 and PDR001 combination HIV testing will be performed at screening for all patients.

[redacted]

7.2.2.5.8 Pregnancy and assessments of fertility

All females of childbearing potential will have a serum pregnancy test within ≤72 hours before first dose of study treatment and during the study at day 1 of each cycle starting from Cycle 2, and at EOT.

In addition, for the FGF401 in combination with PDR001 a urine pregnancy test should be performed every month during and at the end of the safety follow-up period. If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the eCRF.

[redacted]

If a pregnancy test (urine or serum) is positive, but the patient is thought not to be pregnant, study treatment should be stopped until it is determined that the test was falsely positive, and pregnancy is excluded. In case pregnancy is confirmed, study treatment must be permanently discontinued and reporting requirements must be followed as described in Section 8.3.

7.2.2.5.9 Thyroid function – for FGF401 in combination with PDR001 only

Thyroid function assessments outlined in Table 7-4 will be performed as per the schedule provided in Table 7-1.

Following approval of protocol amendment 05, thyroid function assessments will not be performed.

7.2.2.5.10 Cytokines – for FGF401 in combination with PDR001 only

Samples analyzed for the cytokines as outlined in Table 7-5 will be collected at the following time points (Table 7-1):

- Screening
- On an ad-hoc basis in case a patient has an adverse event suspected to be a cytokine release syndrome. In such case, this assessment should be performed at the following time points:
  a. within 5 hours (or as soon as possible) after the occurrence of the adverse event,
  b. one week after the occurrence of the adverse event.

The analysis of the samples will be done only for patients who experienced an adverse event suspected to be a cytokine release syndrome and had follow-up samples collected.

Following approval of protocol amendment 05, no further sample collection will be performed for the cytokine analysis.

7.2.2.6 Cardiac assessments

Following approval of protocol amendment 05, cardiac assessments are not required. These assessments may be performed at the investigator's discretion following local standard of care. When abnormal results constitute an adverse event, they must be recorded on the Adverse Events eCRF.

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12-lead ECG will be performed as per the assessment schedule provided in Table 7-1 and Table 7-6. For all patients, 3 sequential 12-lead ECGs must be performed during screening (or Cycle 1 Day 1 if screening assessment was performed >72 hours prior to first dose) and Cycle 2 Day1. One single ECG will be performed for the other time-points during the trial.

[redacted]

Table 7-6 Central ECG collection plan

Cycle	Day	Time	ECG Measurement
Screening	-	-	Triplicate 12-lead
1	1	Pre-dose	Triplicate 12-lead C1D1 assessment is required only if screening assessment was performed >72 hours prior to first dose.
1[a]	1[a]	2 hr post-dose (±30 minutes)[a]	Triplicate 12-lead[a]
2	1	Pre-dose	Triplicate 12-lead
2	1	2 hr post-dose (±30 minutes)[b]	Triplicate 12-lead
subsequent	1	Pre-dose	Single 12-lead
EOT	-	Anytime	Single 12-lead
Unscheduled	-	Anytime	Single 12-lead
[a] **[For Japan only, ECG is performed additionally at 2 hr post dose (estimated Tmax) on Cycle 1 Day 1]** [b] ECG is performed at 2 hr post-FGF401 administration (estimated Tmax) prior to 2 hr post- FGF401 administration PK sampling completion			

Interpretation of the tracing will be made by a central ECG laboratory. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept as source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF. Such clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant observations occurring after informed consent must be recorded on the Adverse Events eCRF.

7.2.3 Pharmacokinetics and immunogenicity assessments

Serial blood samples will be collected from all patients at all dose levels for the determination of FGF401 plasma concentration. Serum PDR001 concentrations as well as immunogenicity (IG) analysis will be performed for all patients receiving PDR001. The pharmacokinetic (PK) analysis will be performed according to Section 10.5.3.

[redacted]

Following approval of protocol amendment 05, no further blood sample collection will be performed for pharmacokinetics and immunogenicity assessments.

7.2.3.1 Pharmacokinetic blood sample collection and handling

Blood samples will be collected in both the phase I and phase II parts for FGF401 and for PDR001 (as applicable).

The PK blood sampling schedule for all patients receiving FGF401 is outlined in Table 7-7, Table 7-8, Table 7-9 and Table 7-10 and the sampling time points are relative to the time of FGF401 administration.

Blood samples for PDR001 and IG analysis will be collected as outlined in Table 7-11 and Table 7-12. If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for the full PK profile

[redacted]

should be delayed accordingly to match the scheduled time points for Cycle 3 as outlined in Table 7-11 and Table 7-12. PK and IG samples will be collected also in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if immunogenicity by PDR is suspected.

Table 7-7 Phase I parts: Pharmacokinetic blood collection log for QD FGF401 administration

Cycle	Day	Scheduled Time Point	Dose Reference ID	Sample number
1	1	Pre-C1D1 dose/0 hr [a]	1	1
1	1	0.5 hr (±10 minutes)	1	2
1	1	1 hr (±10 minutes)	1	3
1	1	2 hr (±10 minutes)	1	4
1	1	3 hr (±15 minutes)	1	5
1	1	4 hr (±15 minutes)	1	6
1	1	6 hr (±30 minutes)	1	7
1	1	8 hr (±1 hr)	1	8
1	1	12 hr (±2 hr) [b]	1	9
1	2	24 hr/pre-C1D2 dose	1/101	10
1	8	Pre-C1D8 dose/0 hr [a]	2/102 [c]	11
1	8	0.5 hr (±10 minutes)	2	12
1	8	1 hr (±10 minutes)	2	13
1	8	2 hr (±10 minutes)	2	14
1	8	3 hr (±15 minutes)	2	15
1	8	4 hr (±15 minutes)	2	16
1	8	6 hr (±30 minutes)	2	17
1	8	8 hr (±1 hr)	2	18
1	8	12 hr (± 2 hr) [b]	2	19
1	9	24 hr/pre-C1D9 dose	2/103	20
1	15	Pre-C1D15 dose/0 hr [a]	3/104 [c]	21
2	1	Pre-C2D1 dose/0 hr [a]	4/105 [c]	22
2	1	0.5 hr (±10 minutes)	4	23
2	1	1 hr (±10 minutes)	4	24
2	1	2 hr (±10 minutes) [f]	4	25
2	1	3 hr (±15 minutes)	4	26
2	1	4 hr (±15 minutes)	4	27
2	1	6 hr (±30 minutes)	4	28
2	1	8 hr (±1 hr)	4	29
2	1	12 hr (± 2 hr) [b]	4	30
2	2	24 hr/pre-C2D2 dose	4/106	31
3	1	Pre-C3D1 dose/0 hr [a]	5/107 [c]	32
4	1	Pre-C4D1 dose/0 hr [a]	6/108 [c]	33
-	-	Biopsy-matched time point [d]	-	1001+ [e]
-	-	Unscheduled	-	2001+ [e]

[redacted]

Cycle	Day	Scheduled Time Point	Dose Reference ID	Sample number

[a] Take samples immediately prior to the administration of FGF401
[b] Optional and only for the Japanese patients hospitalized according to the local guidance
[c] The first dose reference ID is for current dose, while the second dose reference ID is for last dose the subject received prior to the collection of the PK sample
[d] Time of the blood sample taken close to biopsy sample; this blood sampling needs to be collected within 60 minutes before or after biopsy procedure
[e] Blood samples will be uniquely, sequentially numbered as 1001, 1002, etc and 2001, 2002, etc
[f] Samples will be taken after ECG collection

Table 7-8 Phase II parts: Pharmacokinetic blood collection log for QD FGF401 administration

Cycle	Day	Scheduled Time Point	Dose Reference ID	Sample number
1	1	Pre-C1D1 dose/0 hr [a]	11	101
1	1	1 hr (±10 minutes)	11	102
1	1	2 hr (±10 minutes)	11	103
1	1	6 hr (±15 minutes)	11	104
1	2	24 hr/pre-C1D2 dose	11/201	105
1	8	Pre-C1D8 dose/0 hr [a]	12/202 [b]	106
1	15	Pre-C1D15 dose/0 hr [a]	13/203 [b]	107
2	1	Pre-C2D1 dose/0 hr [a]	14/204 [b]	108
2	1	1 hr (±10 minutes)	14	109
2	1	2 hr (±10 minutes) [e]	14	110
2	1	6 hr (±15 minutes)	14	111
2	2	24 hr/pre-C2D2 dose	14/205	112
3	1	Pre-C3D1 dose/0 hr [a]	15/206 [b]	113
4	1	Pre-C4D1 dose/0 hr [a]	16/207 [b]	114
5	1	Pre-C5D1 dose/0 hr [a]	17	115
6	1	Pre-C6D1 dose/0 hr [a]	18	116
-	-	Biopsy-matched time point [c]	-	3001+ [d]
-	-	Unscheduled	-	4001+ [d]

[a] Take samples immediately prior to the administration of FGF401
[b] The first dose reference ID is for current dose, while the second dose reference ID is for last dose the subject received prior to the collection of the PK sample
[c] Time of the blood sample taken close to biopsy sample; this blood sampling needs to be collected within 60 minutes before or after biopsy procedure
[d] Blood samples will be uniquely, sequentially numbered as 3001, 3002, etc and 4001, 4002, etc
[e] Samples will be taken after ECG collection

Table 7-9 Phase I parts: Pharmacokinetic blood collection log for BID FGF401 administration (if BID dosing is implemented)

Cycle	Day	Scheduled Time Point	Dose Reference ID	Sample number
1	1	Pre-C1D1 dose/0 hr [a]	21	201
1	1	1 hr (±10 minutes)	21	202
1	1	2 hr (±10 minutes)	21	203
1	1	6 hr (±30 minutes)	21	204
1	8	Pre-C1D8 dose/0 hr [a]	22/301 [c]	205
1	8	0.5 hr (±10 minutes)	22	206
1	8	1 hr (±10 minutes)	22	207
1	8	2 hr (±10 minutes)	22	208

[redacted]

Cycle	Day	Scheduled Time Point	Dose Reference ID	Sample number
1	8	3 hr (±15 minutes)	22	209
1	8	4 hr (±15 minutes)	22	210
1	8	6 hr (±30 minutes)	22	211
1	8	8 hr (±1 hr)	22	212
1	15	Pre-C1D15 dose/0 hr [a]	24/302 [c]	213
2	1	Pre-C2D1 dose/0 hr [a]	25/303 [c]	214
2	1	1 hr (±10 minutes)	25	215
2	1	2 hr (±10 minutes) [b]	25	216
2	1	6 hr (±30 minutes)	25	217
3	1	Pre-C3D1 dose/0 hr [a]	27/304 [c]	218
4	1	Pre-C4D1 dose/0 hr [a]	28/305 [c]	219
-	-	Biopsy-matchedtime point [d]	-	5001+ [e]
-	-	Unscheduled	-	6001+ [e]

[a] Take samples immediately prior to the administration of FGF401
[b] Samples will be taken after ECG collection
[c] The first dose reference ID is for current dose, while the second dose reference ID is for last dose the subject received prior to the collection of the PK sample
[d] Time of the blood sample taken close to biopsy sample; this blood sampling needs to be collected within 60 minutes before or after biopsy procedure
[e] Blood samples will be uniquely, sequentially numbered as 5001, 5002, etc and 6001, 6002, etc

Table 7-10 Phase II parts: Pharmacokinetic blood collection log for BID FGF401 administration (if BID dosing is implemented)

Cycle	Day	Scheduled Time Point	Dose Reference ID	Sample number
1	1	Pre-C1D1 dose/0 hr [a]	31	301
1	1	1 hr (±10 minutes)	31	302
1	1	2 hr (±10 minutes)	31	303
1	1	6 hr (±15 minutes)	31	304
1	8	Pre-C1D8 dose/0 hr [a]	32/401 [b]	305
1	15	Pre-C1D15 dose/0 hr [a]	33/402 [b]	306
2	1	Pre-C2D1 dose/0 hr [a]	34/403 [b]	307
2	1	1 hr (±10 minutes)	34	308
2	1	2 hr (±10 minutes) [e]	34	309
2	1	6 hr (±15 minutes)	34	310
2	2	Pre-C2D2 dose/0 hr [a]	35/405 [b]	311
3	1	Pre-C3D1 dose/0 hr [a]	36/404 [b]	312
4	1	Pre-C4D1 dose/0 hr [a]	37/406 [b]	313
5	1	Pre-C5D1 dose/0 hr [a]	38	314
6	1	Pre-C6D1 dose/0 hr [a]	39	315
-	-	Biopsy-matched time point [c]	-	7001+ [d]
-	-	Unscheduled	-	8001+ [d]

[a] Take samples immediately prior to the administration of FGF401
[b] The first dose reference ID is for current dose, while the second dose reference ID is for last dose the subject received prior to the collection of the PK sample
[c] Time of the blood sample taken close to biopsy sample; this blood sampling needs to be collected within 60 minutes before or after biopsy procedure
[d] Blood samples will be uniquely, sequentially numbered as 7001, 7002, etc and 8001, 8002, etc
[e] Samples will be taken after ECG collection

[redacted]

Table 7-11 Schedule of blood (serum) collection for PDR001 PK and IG for patients participating in phase I of FGF401 and PDR001 combination

Cycle*	Day	Scheduled Time Point (h)	Analytes
1	1	0 hr/pre-C1D1 dose[a]	PDR001 and IG
1	1	1 hr (±5 min)[b]	PDR001
1	8	168 hr (±8hr)	PDR001
1	15	336 hr (±24hr)	PDR001
2	1	504 hr (±24hr)/ pre-C2D1 dose[a]	PDR001 and IG
3	1	0hr/pre-C3D1 dose[a]	PDR001 and IG
3	1	1 hr (±5 min)[b]	PDR001
3	15	336 hr (±24hr)	PDR001
4	1	504 hr (±24hr)/ pre-C4D1 dose[a]	PDR001 and IG
5	1	0hr/pre-C5D1 dose[a]	PDR001 and IG
6	1	0hr/pre-C6D1 dose[a]	PDR001 and IG
EOT			PDR001 and IG
150-day safety follow-up**			PDR001 and IG
Unscheduled			PDR001 and IG

*refers to PDR001 administration cycle
**only for patients who come to the site for the 150-day safety follow-up visit
[a] take samples immediately prior to PDR001 infusion
[b] take samples after completion of PDR001 infusion

Table 7-12 Schedule of blood (serum) collection for PDR001 PK and IG for patients participating in Phase II of FGF401 and PDR001 combination

Cycle*	Day	Scheduled Time Point (h)	Analytes
1	1	0 hr/pre-C1D1 dose[a]	PDR001 and IG
1	1	1 hr (±5 min)[b]	PDR001
2	1	0 hr/pre-C2D1 dose[a]	PDR001 and IG
3	1	0 hr/pre-C3D1 dose[a]	PDR001 and IG
3	1	1 hr (±5 min)[b]	PDR001
4	1	0 hr/pre-C4D1 dose[a]	PDR001 and IG
5	1	0hr/pre-C5D1 dose[a]	PDR001 and IG
6	1	0hr/pre-C6D1 dose[a]	PDR001 and IG
EOT			PDR001 and IG
150-day safety follow-up**			PDR001 and IG
Unscheduled			PDR001 and IG

*refers to PDR001 administration cycle
**only for patients who come to the site for the 150-day safety follow-up visit
[a] take samples immediately prior to PDR001 infusion
[b] take samples after completion of PDR001 infusion

The exact date and clock times of drug administration and the actual collection date and time of each sample will be recorded on the appropriate eCRF pages. The timing of meals related to the dose, on days when PK profiles are drawn, should be recorded in the source documents and eCRF. If vomiting occurs within 4 hours following FGF401 administration on the day of PK blood sampling, the clock time of vomiting should be recorded on the corresponding eCRF.

[redacted]

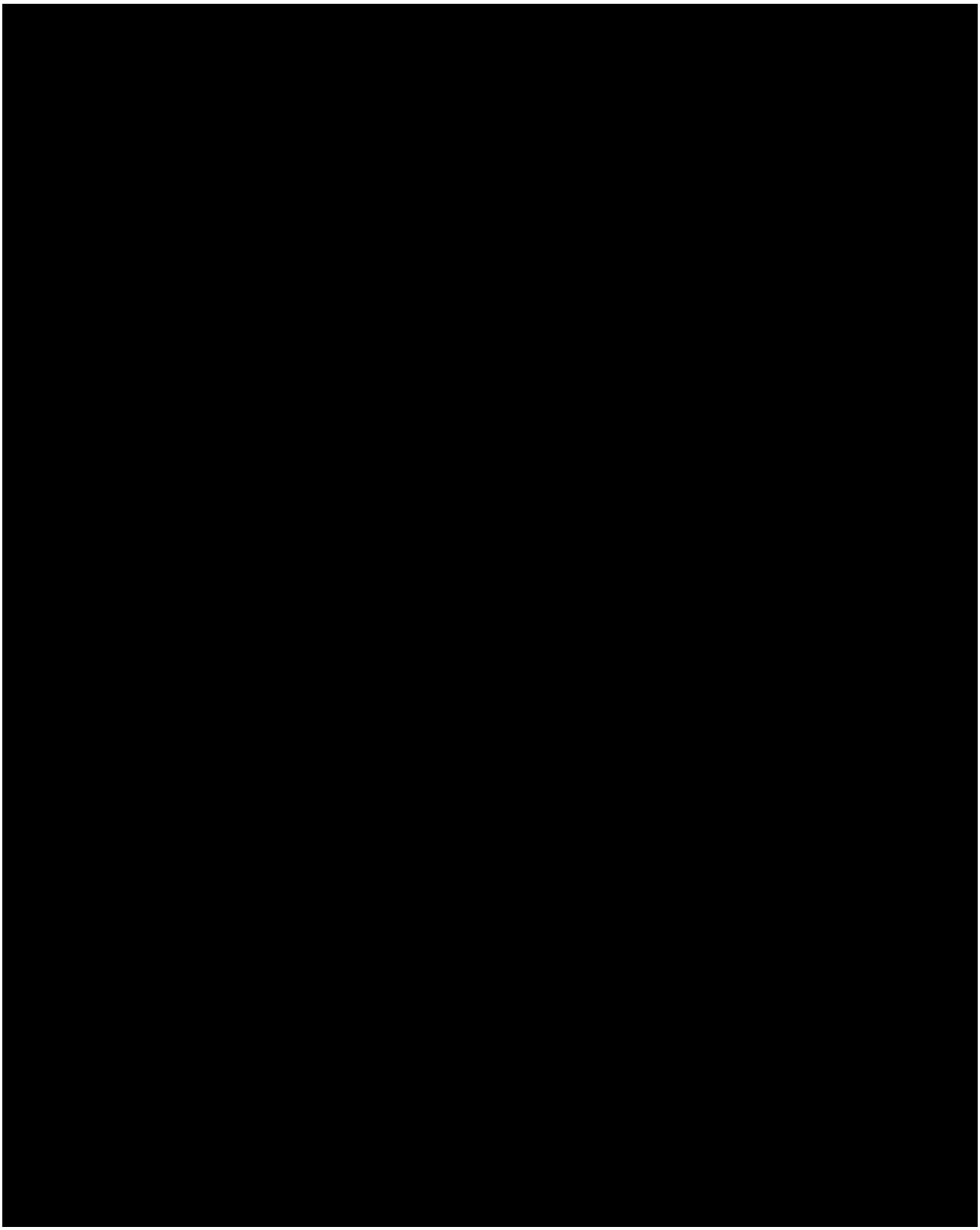
Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood samples should be collected from the arm opposite the one from PDR001 infusion, or from another site, or alternatively the infusion site will need to be flushed with 10mL saline. At specified time points, a total of 3 mL blood will be collected for FGF401 analysis and 2 mL blood for PDR001 as applicable. For time points when PDR001 (mAb) PK and IG are to be measured, a single blood sample of 5 mL in total will be collected. . Refer to the applicable study Laboratory Manual for detailed instructions for the collection, handling and shipment of samples.

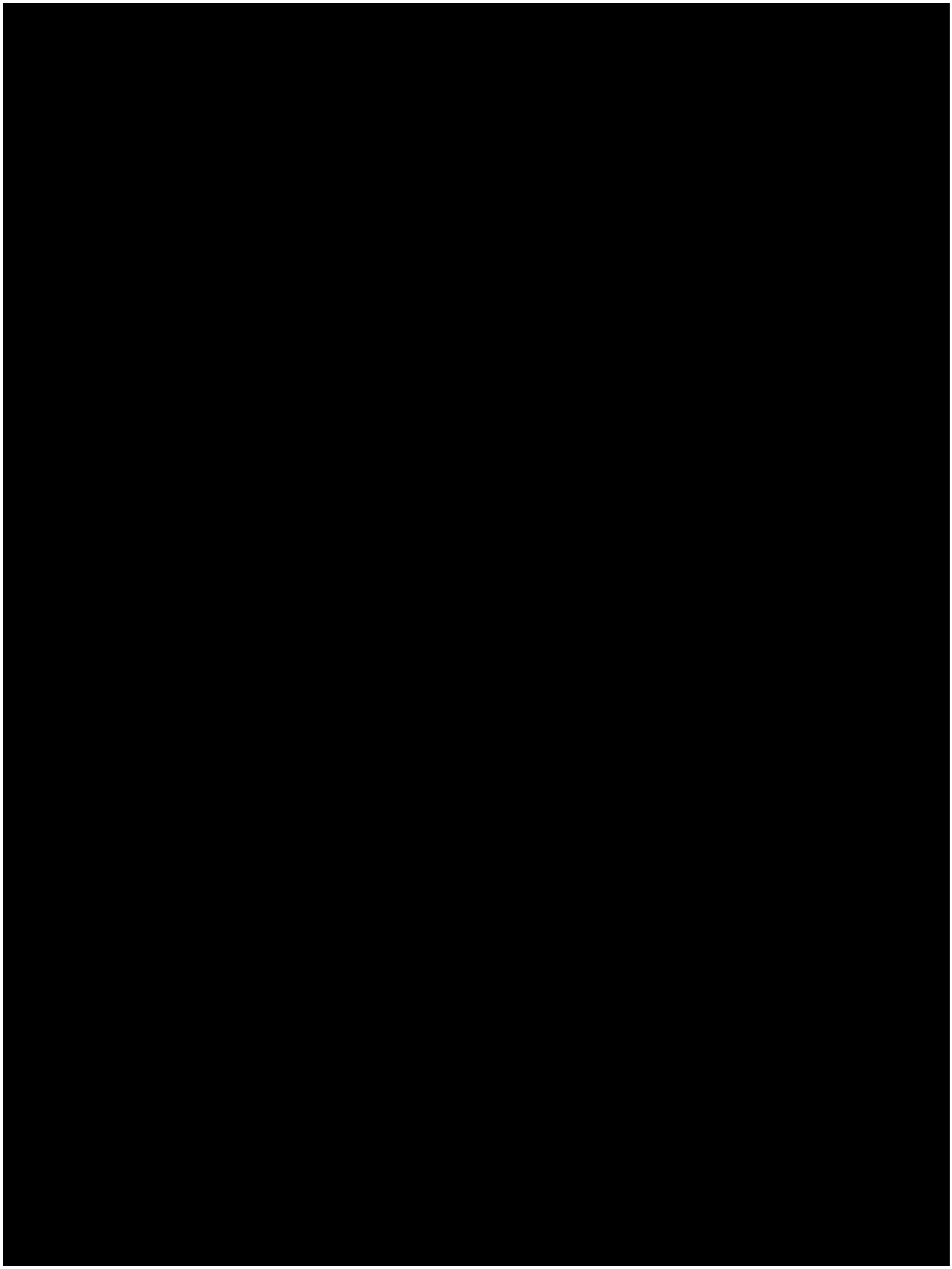
7.2.3.2 Analytical method

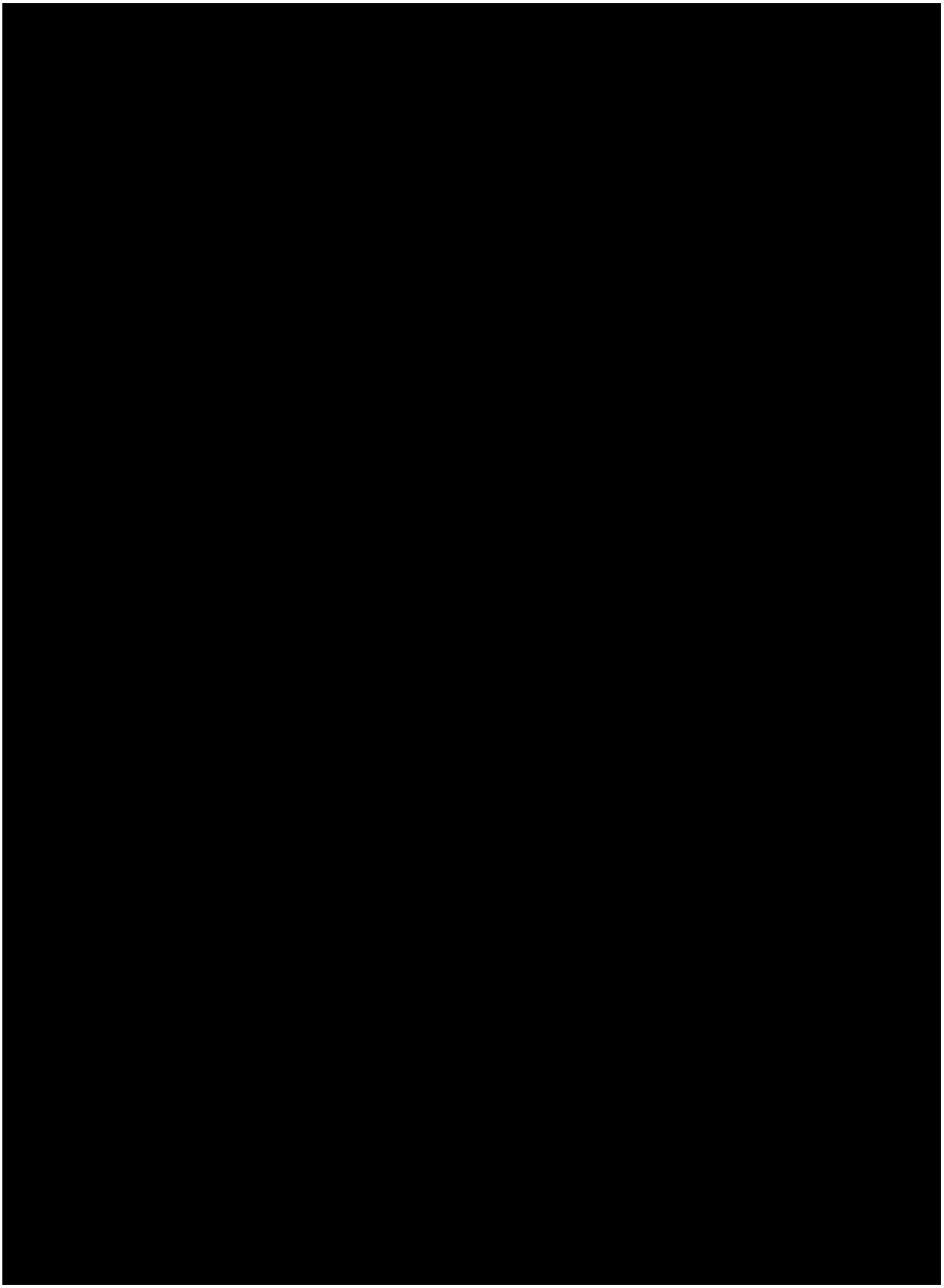
FGF401 and PDR001 concentrations in human plasma and serum will be determined using validated LC-MS/MS assays, respectively. Any results below the lower limit of quantification (LLOQ) and any missing samples will be labeled accordingly.

[redacted]

[redacted]







8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

For patients who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event eCRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 150 days following the last dose of PDR001 (for patients who have been treated with PDR001), or at least 30 days following the last dose of FGF401 (Section 7.1.6). Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Events eCRF.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST or irRC criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

[redacted]

  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

For patients who sign the molecular pre-screening ICF (applicable only for Phase 1 and Group 3 in Phase II of FGF401 single agent and for Stage 2 of the FGF401 and PDR001 combination should it proceed), SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular pre-screen failure), SAE collection ends 30 days after the last study related procedure.

For all other patients who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 150 days following the last dose of PDR001 (for patients who have been treated with FGF401 and PDR001 combination), or at least 30 days after discontinuation of FGF401 (for patient who have been treated with FGF401 single agent), must be reported to Novartis within 24 hours of learning of its occurrence. If a patient starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

Any SAEs experienced after the above defined period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Any additional information for the SAE including recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

[redacted]

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, a Novartis Chief Medical Office and Patient Safety department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

Study treatment must be stopped if a patient becomes pregnant.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. After the mother has provided consent, the newborn will be followed-up for 12 months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to Novartis Chief Medical Office and Patient Safety (CMOPS&). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure's. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

Phase I Parts:

A data monitoring board will not be used for this study. This is an open-label, Phase I/II study and Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference, the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the

[redacted]

first cycle of treatment, and all available PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the Bayesian model's (with EWOC) recommendation, and a medical review of relevant clinical, PK, [redacted] and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD and/or RP2D, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level, see Section 10.4.2.1.

Phase II Parts:

An independent data monitoring committee will not be formed for this exploratory phase II parts of the study. Individual patient data will be reviewed on an ongoing basis and aggregate safety data and the primary endpoint will be monitored frequently by the study team across the duration of the trial. The data review and analysis will be based on the available data in the clinical database at the respective time.

8.6 Steering Committee

A Steering Committee constituted of members of the Translational Clinical Oncology Leadership Team will be formed for this study. If the monitoring of the study data requires a decision to be taken on the continuation of the study, then the relevant data (e.g., safety data or primary analysis and predictive probability of success (PPOS)) will be communicated to the Steering Committee for decision making purposes.

In the Phase II part of the FGF401 in combination with PDR001, an interim analysis for efficacy and futility will be performed after the first 35 patients have been enrolled and have had at least one-post treatment tumor evaluation or discontinued earlier (Stage 1). Interim decision making will be based on the Bayesian posterior probability of ORR and posterior median ORR. The interim analysis of ORR will be based on unconfirmed response. The phase II part in the combination arm will be stopped due to efficacy if the posterior probability of ORR in the unselected population included in the no/limited anti-tumor activity interval [0, 0.15) is less than 0.10 and the posterior median ORR is 0.30 or more. Considering the exploratory nature of the study, when the aforementioned success criteria are not met but the evaluation of overall efficacy and safety suggests the treatment is promising for development, decision of stop at Stage 1 for success can also be made by Novartis.

Should the study not stop at Stage 1 for success in the unselected HCC population, go/no go decision to Stage 2 will be made by evaluating the anti-tumor activity in subgroups defined by FGF19 expression and/or FGF19 pathway activation based on the predictive probability of ORR. For an individual subgroup, if that predictive probability to not meet the efficacy criteria (i.e. posterior probability of ORR included in the no/limited anti-tumor activity interval is less than 0.10 and the posterior median ORR is 0.30 or more) at the final analysis is not greater than 0.90, and the number of patients in the subgroup is less than 25, the study will move to Stage 2 and more patients will be enrolled to the subgroup until a sample size of approximately 25 is reached. If 25 or more patients are already enrolled to the subgroup at the time of interim

[redacted]

analysis, interim analysis will be performed but no further enrollment will be allowed in that subgroup.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the

patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Blood and tumor samples for PK [redacted] will be collected by sites and sent to a Central laboratory for processing. The Laboratory results will be sent electronically to Novartis. Radiological and photography data will be acquired by the sites and interpreted locally. Details regarding all CRO procedures including collection and shipment of data will be described in the manual provided by the respective CRO. ECG data collected during the study will be reviewed and processed centrally by a specialist CRO.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

PK [redacted] samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). At some sites, part(s) of the hospital data may also be processed centrally.

After the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Oncology Translational Medicine.

[redacted]

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetics (PK) [redacted] measurements. Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data, summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. In addition, individual listings of all raw data captured in the clinical database will be presented by treatment group and patient.

All data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. The following rules will be followed for reporting results unless otherwise stated:

- Phase I part: Patients with the same dose level, feeding regimen and schedule of FGF401 single agent or FGF401 in combination with PDR001 will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group, unless otherwise stated.
- Phase II part: Patients will be analyzed according to the Group to which they were assigned for FGF401 single agent. For FGF401 in combination with PDR001, if subgroups based on FGF19 expression and/or pathway activation are identified, patients will be analyzed according to the subgroup. All summaries, listings, figures and analyses will be performed by Group (FGF401 single agent) or subgroup (FGF401 in combination with PDR001), unless otherwise stated.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected according to Section 7.1.2.1 will not be included in any analysis, but will be reported in the CSR as separate listings.

The study data will be analyzed and reported based on all patients' data of the phase I and the phase II parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported following the end of study (refer to Section 4.3 for definition).

Details of the statistical analysis and data reporting will be provided in the Novartis Report and Analysis Plan (RAP) document finalized prior to database lock.

10.1 Analysis sets

10.1.1 Full Analysis Set

The full analysis set (FAS) comprises all patients who received at least one dose of study medication. Patients enrolled in the phase I part will be analyzed according to the treatment they have been assigned to. Patients enrolled in the phase II part will be analyzed by Group. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

[redacted]

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients enrolled in the phase I part will be analyzed according to the study treatment (regimen) they actually received. Patients enrolled in the phase II part will be analyzed by Group.

A precise definition of "actually received" will be added in the RAP.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of a subset of patients from the FAS who have an adequate tumor assessment at baseline and at least one post treatment tumor assessment with a result other than UNK, and no major protocol deviations.

All major protocol deviations leading to exclusion from the PPS will be detailed in the RAP.

The PPS will be used in the phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint (see Section 10.4). If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.1.4 Dose-determining analysis set

The dose-determining analysis set (DDS) consists of all patients from the safety set from the Phase I parts who either meet the following minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during the applicable evaluation period of DLTs.

FGF401 single agent

A patient is considered to have met the minimum exposure criterion if he/she received at least 66% of the planned doses of FGF401 in the first cycle of dosing i.e. at least 14 out of the 21 full planned daily dose of FGF401.

Patients who do not experience DLT during the first cycle of treatment are considered to have sufficient safety evaluations if they have been observed for ≥ 21 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

FGF401 in combination with PDR001

A patient is considered to have met the minimum exposure criterion if he/she received at least 66%, (i.e. at least 28 days) of the planned doses of FGF401, and all planned doses of PDR001 in cycle 1 and cycle 2 of dosing.

Patients who do not experience DLT during the first 2 cycles of treatment are considered to have sufficient safety evaluations if they have been observed for ≥ 42 days following the first dose, and are considered by both Novartis and Investigators to have enough safety data to conclude that a DLT did not occur.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) includes all subjects who provide at least one evaluable drug concentration. For those requiring non-compartment analyses, the PAS includes all

[redacted]

subjects who provide an evaluable PK profile. Patients will be removed from the determination of individual PK parameters on a case by case basis (to be described in detail in the Clinical Study Report).

The PAS will be used for summaries of drug concentration data, non-compartment PK analysis and/or population PK analysis. The analysis of the food effect on the FGF401 PK exposures will also use the PAS.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively using the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses of treatments.

10.3.1 Study treatment

Duration of exposure to FGF401 and PDR001and as well as the actual total dose, the dose intensity (calculated as the ratio of actual dose received to actual duration) and the relative dose intensity (calculated as the ratio of dose intensity to planned dose received/planned duration) of the study treatment will be summarized descriptively.

Categories for relative dose intensity of FGF401 and PDR001 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients falling in each category will be presented.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by Anatomic-Therapeutic-Chemical classification (ATC) term.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized by treatment group for the FAS.

10.4 Primary objective

Phase I parts

The primary objective is to determine the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) of single agent FGF401 and FGF401 in combination with PDR001.

[redacted]

Phase II parts

For FGF401 single agent, the primary objective is to assess preliminary anti-tumor activity in the following three groups of patients:

- Group 1: HCC patients from Asian countries
- Group 2: HCC patients from non-Asian regions
- Group 3: patients who have other solid tumors regardless of geography and positive FGFR4/KLB expression

For FGF401 in combination with PDR001, the primary objective is to assess the preliminary anti-tumor activity of this combination in adult patients with HCC.

10.4.1 Variable

Phase I parts

The primary endpoint is the incidence of dose limiting toxicities (DLTs). For FGF401 single agent and in combination with PDR001, respectively, estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT during the evaluation period for patients in the DDS. This probability is estimated by the corresponding model described in Section 10.4.2.

Phase II parts

Group 1 and 2-FGF401 single agent: The primary endpoint is time to progression (TTP), as per local assessment, defined as the time from the date of baseline evaluation to the date of the first documented event that the radiological confirmation of disease progression or death due to underlying cancer (RECIST v1.1).

Group 3-FGF401 single agent: The primary endpoint is overall response rate, defined as the proportion of patients having a best overall response of either complete response (CR) or PR at any time on study as per local assessment according to RECIST v1.1.

FGF401 and PDR001 combination: The primary endpoint is overall response rate, defined as the proportion of patients having a best overall response of either CR or PR at any time on study as per local assessment according to RECIST v1.1.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 FGF401 single agent

Phase I part

A Bayesian hierarchical logistical regression model (BHLRM) will be applied to estimate the relationship between dose and the probability of a patient experiencing a dose limiting toxicity (DLT) for patients in fasted condition (stratum 1) and in fed condition (stratum 2). The standard Bayesian hierarchical model assumes full exchangeability of strata parameters; for the methodology and an application to binary data see Thall et al. 2003 and Chugh et al. 2009. Here, we extend the standard Bayesian hierarchical model to dose-toxicity data, and exchangeable as well as non-exchangeable strata parameters.

[redacted]

For the two patient strata, the probability of experiencing a DLT is modeled as follows:

$$\text{logit}(\pi^d_{fasted}) = \log(\alpha_{fasted}) + \beta_{fasted}\log(d/d^*)$$

$$\text{logit}(\pi^d_{fed}) = \log(\alpha_{fed}) + \beta_{fed}\log(d/d^*)$$

where d denotes dose; d^* is a fixed reference dose; π^d_{fasted} and π^d_{fed} are the probability of a patient experiencing a DLT at dose d in respectively fasted and fed conditions; and the two parameter vectors $\theta_{fasted} = (log(\alpha_{fasted}), log(\beta_{fasted}))$ and $\theta_{fed} = (log(\alpha_{fed}), log(\beta_{fed}))$ describe the relationship between dose and toxicity for the two strata.

We further let the parameter vectors θ_{fasted} and θ_{fed} be either exchangeable or non-exchangeable, with probability p and $(1-p)$, respectively.

1. Under exchangeability, the parameter vectors θ_{fasted} and θ_{fed} are assumed to follow a bivariate normal distribution:

$$\theta_{fasted}\ ,\quad _{fed} \sim BVN(\mu_{exch}, \boldsymbol{\Sigma}_{exch}),$$

where $\boldsymbol{\mu}_{exch} = (\mu_{e1}, \mu_{e2})$ and $\boldsymbol{\Sigma}_{exch} = \begin{pmatrix} \tau^2_{e1} & \rho\tau_{e1}\tau_{e2} \\ \rho\tau_{e1}\tau_{e2} & \tau^2_{e2} \end{pmatrix}$ are the mean vector and covariance matrix.

Prior distributions for μ_{exch} and $\boldsymbol{\Sigma}_{exch}$ of the exchangeability distribution complete the model specifications for the exchangeability component of the model

The prior distributions for the component of μ_{exch} will be normal and the prior distributions for the standard deviations and the correlation in $\boldsymbol{\Sigma}_{exch}$ will be log-normal and uniform, respectively.

2. Under non-exchangeability, the parameter vectors θ_{fasted} and θ_{fed} are assumed to have a weakly informative bivariate normal prior distribution.

$$\theta_{fasted}\ , \theta_{fed} \sim BVN(m_w, \mathrm{S}_w),$$

where $\mathbf{m}_w = (m_{w1}, m_{w2})$ and $\mathbf{S}_w = \begin{pmatrix} \tau^2_{w1} & c\tau_{w1}\tau_{w2} \\ c\tau_{w1}\tau_{w2} & \tau^2_{w2} \end{pmatrix}$ are the mean vector and covariance matrix.

The specification of prior distributions is described in Appendix 10.

Change in dosing schedule

In the event of a change in dosing schedule, a new BLRM will be set up. This new BLRM will have the same functional form as that described above and will incorporate existing dose escalation data in the prior distributions. For comparability, doses for the new and old model will be normalized to dose in mg per day.

Dose recommendation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels for fasted and fed conditions are obtained. The results of this analysis are

[redacted]

summarized in terms of the probabilities that the true rate of DLT for fasted and fed conditions at each dose-level will lie within each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1.00] excessive toxicity

The overdose control criterion mandates that under each of the patient conditions, any dose of FGF401 for which the DLT rate has more than a 25% risk of being excessively toxic, i.e. P(DLT) is 0.33 or higher, will not be considered for the next dose cohort. The final estimate of the MTD/RP2D will also satisfy this condition.

Details of the criteria for dose escalation and the estimation of the MTD are provided in Section 6.2.3.

Summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class and preferred term. The dose-determining analysis set will be used for these summaries.

Phase II part

The FAS will be used for the primary analysis.

Group 1 and 2: The distribution of TTP will be estimated using the Kaplan-Meier method. A positive trend regarding the activity of FGF401 will be concluded if the observed lower limit of one-sided 90% confidence interval (CI) of TTP $\geq$ 1.5 months (Group 1) and 2.2 months (Group 2), which are the expected median TTPs without FGF401 treatment in group 1 and 2, respectively. The median TTP and quantiles (along with one-sided 90% CI) will be presented. The Kaplan-Meier curve will be presented graphically. TTP rate estimates (along with one-sided 90% CI) at 1.5, 3 and 6 months will be presented, as given by the Kaplan-Meier analysis.

Group 3: BOR, defined in Appendix 1, will be summarized by tumor type. The number (%) of patients having BOR as CR, PR, SD, PD and unknown per RECIST 1.1 will be provided. The overall response rate (ORR), the proportion of patients having BOR of either CR or PR, of an individual tumor type will be summarized if the number of observations is reasonable large.

10.4.2.2 FGF401 in combination with PDR001

Phase I part

A 5-parameter adaptive Bayesian logistic regression model (BLRM), guided by the EWOC principle will be used to make dose recommendations and estimate the MTD/RDE of the combination.

The respective single agent dose-DLT relationships are defined as follows:

FGF401: $\text{logit}\left(\pi_1(d_1)\right) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

PDR001: $\text{logit}\left(\pi_2(d_2)\right) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

[redacted]

Where, $\pi_1(d_1)$ and $\pi_2(d_2)$ are respectively the probability that a patient has a DLT during the first 2 cycles of combination treatment with FGF401 and PDR001 given at the Q3W dose d_1 and d_2 respectively, and d_1^*=120 mg and d_2^*=300 mg are respectively the FGF401 and PDR001 reference doses. α_i, $\beta_i > 0$ are the parameters of the model.

Then, the dose-DLT relationship of the combination FGF401 + PDR001 is defined as follows:

$$Odds\left(\pi_{12}(d_1, d_2)\right) = \frac{\pi_{12}(d_1, d_2)}{1 - \pi_{12}(d_1, d_2)} = \exp(\eta \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}) \left[\frac{\pi_1(d_1) + \pi_2(d_2) - \pi_1(d_1)\pi_2(d_2)}{(1 - \pi_1(d_1))(1 - \pi_2(d_2))}\right]$$

Where η is the log-odds ratio between the interaction and no-interaction model at the reference doses. Here $\eta = 0$ corresponds to no-interaction, $\eta > 0$ represents synergistic toxicity, and $\eta < 0$ represents antagonistic toxicity. The specification of prior distributions is described in Appendix 10.

Change in dosing schedule

In the event of a change in dosing schedule, a new BLRM will be set up. This new BLRM will have the same functional form as that described above and will incorporate existing dose escalation data in the prior distributions.

Dose recommendation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels for FGF401 in combination with PDR001 are obtained. The results of this analysis are summarized in terms of the probabilities that the true rate of DLT for FGF401 in combination with PDR001 at each dose-level will lie within each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1.00] excessive toxicity

The overdose control criterion mandates that under each of the patient conditions, any dose of FGF401 for which the DLT rate has more than a 25% risk of being excessively toxic, i.e. P(DLT) is 0.33 or higher, will not be considered for the next dose cohort. The final estimate of the MTD/RP2D will also satisfy this condition.

Details of the criteria for dose escalation and the estimation of the MTD are provided in Section 6.2.3.

Summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class and preferred term. The dose-determining analysis set will be used for these summaries.

Phase II part

The FAS will be used for the primary analysis.

The number (%) of patients having BOR as CR, PR, SD, PD and unknown per RECIST 1.1 will be provided. The overall response rate (ORR), the proportion of patients having BOR of either CR or PR, will be summarized.

[redacted]

If at interim analysis the efficacy is declared (for more details, refer to Section 10.7.2), the primary analysis will be overall. In addition, summary by subgroup(s) defined by FGF19 expression and/or FGF19 pathway activation will be conducted as an exploratory analysis. If at interim analysis the efficacy is not declared, the primary analysis will be done by subgroup(s) defined by the FGF19 expression and/or FGF19 pathway activation.

A Bayesian method will be used in order to estimate the distribution of the ORR and to provide inferential summaries (mean, median, interval probabilities). A minimally informative Beta prior distribution (Neuenschwander 2008) with b = 1 and a = 3/7 is specified for the ORR assuming the true mean ORR is 30%.

Anti-tumor activity is classified based on ORR intervals as following:

- [0, 0.15) no/limited anti-tumor activity
- [0.15, 0.30) moderate anti-tumor activity
- [0.30, 1.00] clinically significant anti-tumor activity

10.4.3 Handling of missing values/censoring/discontinuations

Phase I parts

Patients in the phase I parts who are ineligible for the DDS will be excluded from the primary analysis, although their additional data (e.g., safety, PK, [redacted] efficacy etc.) will be used in the review of patient data at the dose-escalation meeting. Missing data will simply be treated as missing on appropriate tables/listings.

Phase II parts

FGF401 single agent Group 1 and 2: If a patient has not had the event at the date of analysis cut-off or when he/she received any further anti-neoplastic therapy, TTP will be censored at the time of the last adequate assessment before the cut-off date, or start date of other anti-neoplastic therapy.

FGF401 single agent Group 3 and FGF401 and PDR001 combination treatment group: BOR will be considered missing if the patient does not have both baseline and at least one post-baseline RECIST assessment by the investigator, allowing the assignment of a BOR under RECIST 1.1 (see Appendix 1). For ORR calculation, patients who have missing BOR will be considered as non-responder (non-CR/PR).

10.4.4 Supportive analyses

For the phase II parts, the analyses of the primary endpoint will be repeated using the PPS, if PPS is different from FAS.

For the FGF401 in combination with PDR001, the same analyses will be performed using the tumor response evaluation as per irRC (Appendix 9).

For the FGF401 in combination with PDR001, supportive analysis by geographical region (Asian vs. non-Asian) will be performed for key efficacy endpoints.

[redacted]

Additional supportive or exploratory analyses will be conducted to support the primary objective if appropriate and details of the analysis will be defined in the Reporting and Analysis Plan (RAP).

10.5 Secondary objectives

Please refer to Section 3 for the secondary objectives.

10.5.1 Efficacy objectives

For all efficacy analyses, the FAS will be used unless otherwise specified.

Phase I parts

BOR, ORR and DCR will be summarized by treatment group.

The Kaplan-Meier plot for TTP at the MTD/RP2D will be presented. The estimated TTP rate at the MTD/RP2D along with 95% CI at 1.5, 3 and 6 months will be presented. If appropriate, the Kaplan-Meier plots for OS at the MTD/RP2D will also be presented. These analyses will only be provided if there are at least 10 enrolled patients at MTD/RP2D. Otherwise, data will only be listed.

Phase II parts

FGF401 single agent- Group 1 and 2: BOR, ORR and DCR will be summarized by treatment group.

The Kaplan-Meier plot for OS will be presented by group, and by FGF19 status within individual HCC groups. The estimated OS rate along with 95% CI at 3, 5, 7 and 9 months will be presented by group.

FGF401 single agent- Group 3: BOR and DCR will be summarized by tumor type.

The Kaplan-Meier analysis for PFS and OS will be provided by tumor type. This analysis will only be provided for tumor type with which there are at least 10 enrolled patients. Otherwise, data will only be listed.

FGF401 and PDR001 combination: The Kaplan-Meier analysis for TTP, PFS, OS and DOR will be provided. BOR and DCR will be summarized. The same analyses will be performed using the tumor response evaluation as per irRC (Appendix 9).

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used unless otherwise specified. Listings and summary tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's pre-screening informed consent to the day before first dose of study medication

[redacted]

2. on-treatment period: from day of first dose of study medication to 30 days after the last dose of study medication
3. -For patients receiving FGF401 single agent: post-treatment period: starting at day 31 after last dose of study medication.

   -For patients receiving FGF401 in combination with PDR001: extended safety follow-up period: starting at day 31 after last dose of study medication, ending at least 150 days after last dose of PDR001.

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades) and relation to study treatment.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

For patients receiving FGF401 in combination with PDR001, additional summaries of related AEs, related SAEs, and related AESIs will be produced covering all events with onset or worsening at any time during the extended safety follow-up period.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, laboratory data will be graded accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

[redacted]

- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

10.5.2.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.2.5 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized.

10.5.3 Pharmacokinetics

The PAS will be used in the pharmacokinetic data analysis and PK summary statistics.

Concentration data will be listed by time point, patient and treatment group. Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for PDR001 and FGF401 concentrations will be presented at each scheduled timepoint by treatment.

All concentration data for PDR001 and FGF401 will be displayed graphically. Individual concentration-time profile as well as mean concentration-time profile will be plotted.

PK parameters will be determined for all PK-evaluable patients with noncompartmental method(s) using Phoenix WinNonlin version 6.2 or above (Pharsight, Mountain View, CA). Exploratory population PK analyses will be conducted to derive PK parameters using compartmental modeling method when necessary. For FGF401, the PK parameters include but may be not limited to those listed in Table 10-1. For PDR001, PK parameters would be limited to Cmax, Tmax, AUClast and Ctrough. The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented by treatment for all PK parameters defined in Table 10-1 except Tmax, where only n, median, minimum and maximum will be presented. Missing data will not be imputed.

[redacted]

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume^{-1})
Cmax	The maximum (peak) observed plasma drug concentration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma drug concentration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The apparent total body clearance of drug from the plasma after oral administration (vol x time^{-1})
Racc	Accumulation ratio calculated using AUCtau at steady state divided by AUCtau at day 1

10.5.3.1 Data handling principles

Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. For FGF401, samples taken from patients who vomited within 4 hours of dosing may be excluded from the analysis.

All concentrations below their respective LLOQs (lower limits of quantification) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters.

10.5.3.2 Data analysis principles

10.5.3.2.1 Summary tables and figures

The individual plasma concentration time profiles and mean concentration time profile of analytes will be summarized descriptively and graphically by treatment group in phase I part and group in phase II part.

Descriptive statistics of PK parameters shown in Table 10-1 will be provided if appropriate.

Further graphical exploratory analyses will be carried out if deemed appropriate.

10.5.3.2.2 Dose proportionality

The assessment of dose proportionality will be conducted for AUC and Cmax of FGF401 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% CI of the slope for each parameter will be computed from the model and presented in the summary table. The dose proportionality assessment is exploratory analysis due to insufficient power to demonstrate dose proportionality.

10.5.3.2.3 Food effect

As exploratory analysis to assess the food effect on FGF401 pharmacokinetics, exposure measures (Cmax, Tmax and AUC) will be compared among patients taking study drug under different feeding regimens (fasted or fed) as appropriate.

[redacted]

[redacted]

10.5.3.2.5 Immunogenicity

Immunogenicity of PDR001 will be characterized descriptively by tabulating antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment. The impact of ADA on the occurrence of safety endpoints, efficacy endpoints, and PDR001 PK will be assessed using appropriate methods. Further details will be provided in the SAP or in a stand-alone analysis plan document.

[redacted]

10.7 Interim analysis

10.7.1 FGF401 single agent

Phase I part

No formal interim analysis is planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation part, the next dose will be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in Section 6.2.3.

Phase II part

No formal interim analysis is conducted. However, individual patient data will be reviewed on an ongoing basis by the study team across the duration of the trial (Section 8.5 and Section 8.6).

[redacted]

10.7.2 FGF401 in combination with PDR001

Phase I part

No formal interim analysis is planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation part, the next dose will be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in Section 6.2.3.

Phase II part

An interim analysis for efficacy and futility will be performed after the first 35 patients have been enrolled and have had at least one-post treatment tumor evaluation or discontinued earlier (Stage 1). Interim decision making will be based on the Bayesian posterior probability of ORR and posterior median ORR. The interim analysis of ORR will be based on unconfirmed response. The phase II part in the combination arm will be stopped due to efficacy if the posterior probability of ORR in the unselected population included in the no/limited anti-tumor activity interval [0, 0.15) is less than 0.10 and the posterior median ORR is 0.30 or more. Considering the exploratory nature of the study, when the aforementioned success criteria are not met but the evaluation of overall efficacy and safety suggests the treatment is promising for development, decision to stop at Stage 1 for success can also be made by Novartis.

Should the study not stop at Stage 1 for success in the unselected HCC population, go/no go decision to Stage 2 will be made by evaluating the anti-tumor activity in subgroups defined by FGF19 expression and/or FGF19 pathway activation based on the predictive probability of ORR. For an individual subgroup, if that predictive probability to not meet the efficacy criteria (i.e. posterior probability of ORR included in the no/limited anti-tumor activity interval is less than 0.10 and the posterior median ORR is 0.30 or more) at the final analysis is not greater than 0.90, and the number of patients in the subgroup is less than 25, the study will move to Stage 2 and more patients will be enrolled to the subgroup until a sample size of approximately 25 is reached. If 25 or more patients are already enrolled to the subgroup at interim analysis, interim analysis will be performed but no further enrollment will be allowed in that subgroup.

10.8 Sample size calculation

10.8.1 FGF401 single agent

10.8.1.1 Phase I part

Initially, cohorts of 1 to 6 evaluable patients will be enrolled in the phase I part. Upon observation of specific toxicities (see Section 6.2.3 for details), cohorts of 3 to 6 evaluable patients will be enrolled including at least six evaluable patients at the MTD/RP2D level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 evaluable patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 21 evaluable patients are expected to be treated in the phase I part, for the model to have reasonable operating characteristics relating to its MTD and/or RP2D recommendation.

[redacted]

10.8.1.2 Phase II part

Group 1

Group 1 is designed to assess the preliminary anti-tumor activity of FGF401 in HCC patients with positive expression of FGFR4 and KLB from Asian countries. If the lower limit of one-sided 90% CI of TTP is equal to or greater than 1.5 months, which is the expected median TTP without FGF401 treatment, it will be considered as preliminary evidence of clinically relevant efficacy of FGF401 in Group 1.

It is assumed that TTP has an exponential distribution and the true median TTP with FGF401 treatment is 3.0 months, which is considered a clinically relevant improvement with treatment in this patient population, and the enrollment rate is 3.5 patients per month. Analysis will be provided when all patients have potentially completed at least six cycles of treatment or discontinued the study. Table 10-2 shows the probability of success (PoS), i.e., the probability of the lower limit of observed one-sided 90% CI of TTP equal to or greater than 1.5 months, calculated by simulation given these assumptions and different sample sizes.

Approximately 40 patients will be enrolled, however, more patients with double positive tumors may be enrolled if the emerging clinical data supports, see Section 4.1. Considering a drop-out rate of 15%, the PoS is 90.6%.

Table 10-2 Probability of Success under different number of sample size in Group 1 (drop rate = 15%)

Sample size	Expected number of events	P (lower limit of one-sided 90% CI ≥1.5)
30	20.4	0.833
35	24.2	0.888
40	28.9	0.906

Group 2

Group 2 is designed to assess the preliminary anti-tumor activity of FGF401 in HCC patients with positive expression of FGFR4 and KLB from non-Asian regions. If the lower limit of one-sided 90% CI of TTP is equal to or greater than 2.2 months, which is the expected median TTP without FGF401 treatment, it will be considered as preliminary evidence of clinically relevant efficacy of FGF401 in Group 2.

It is assumed that TTP has an exponential distribution and the true median TTP with FGF401 treatment is 4.2 months, which is considered a clinically relevant improvement with treatment in this patient population, and the enrollment rate is 3.5 patients per month. Analysis will be provided when all patients have potentially completed at least six cycles of treatment or discontinued the study. Table 10-3 shows the PoS, i.e., the probability of the lower limit of observed one-sided 90% CI of TTP equal to or greater than 2.2 months, calculated by simulation given these assumptions and different sample sizes.

Approximately 40 patients will be enrolled, however, more patients with double positive tumors may be enrolled if the emerging clinical data supports, see Section 4.1. Considering a drop-out rate of 15%, the PoS is 87.7 %.

[redacted]

Table 10-3 Probability of Success under different number of sample size in Group 2 (drop rate = 15%)

Sample size	Expected number of events	P (lower limit of one-sided 90% CI ≥ 2.2)
30	17.8	0.800
35	21.2	0.857
40	25.6	0.877

Group 3

Group 3 is designed to assess the preliminary anti-tumor activity of FGF401 in other solid tumors with positive expression of FGFR4 and KLB. Overall approximately 20 patients are planned to be enrolled. Table 10-4 shows the probabilities of observing at least a certain number of responders given different values of true ORR.

If the true ORR of a tumor type is 0.05, 0.10 and 0.25, the probabilities of observing 1 or more responders with 20 patients are 0.642, 0.878 and 0.997, respectively.

Table 10-4 Cumulative probability (upper tail) of responses observed or more given true ORR and 20 patients

True ORR (p)	Responses observed (n)	P (responses≥ n | N=20, p)
0.05	1	0.642
	2	0.264
	3	0.075
	4	0.016
0.10	1	0.878
	2	0.608
	3	0.323
	4	0.133
	5	0.043
	6	0.011
0.25	1	0.997
	2	0.976
	3	0.909
	4	0.775
	5	0.585
	6	0.383

10.8.2 FGF401 in combination with PDR001

10.8.2.1 Phase I part

Cohorts of 3 to 6 evaluable patients will be enrolled including at least six evaluable patients at the MTD/RP2D level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 evaluable patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 12 evaluable patients are expected to be treated in the phase I part, for the model to have reasonable operating characteristics relating to its MTD and/or RP2D recommendation.

[redacted]

10.8.2.2 Phase II part

The phase II part is designed to assess the preliminary anti-tumor activity of FGF401 in combination with PDR001 in HCC patients. If the posterior probability of ORR in the unselected population included in the no/limited anti-tumor activity interval [0, 0.15) is less than 0.10 and the posterior median ORR is 0.30 or more, it will be considered as preliminary evidence of clinically relevant efficacy of FGF401 in combination with PDR001.

At interim analysis, if the predictive probability of ORR (based on unconfirmed response) to not be considered as preliminary evidence of clinically relevant efficacy defined above at the final analysis is more than 0.90, that subgroup will not be open for further enrolment. If 25 or more patients are already enrolled to the subgroup, interim analysis will be performed but no further enrollment will be allowed in that subgroup.

In order to show how the design performs, simulation studies are conducted assuming 35 patients are enrolled in the Stage 1, and the biopsy failure rate is 15%. In addition, due to the uncertainty of the proportions of FGF19 positive and FGF19 negative patients (per FGF19 expression and/or FGF19 pathway activation status), the following 2 scenarios are investigated: (1) the percentages of FGF19 positive and FGF19 negative patients enrolled in the Stage 1 are 20% and 80% respectively, and (2) the percentages of FGF19 positive and FGF19 negative patients enrolled in the Stage 1 are 40% and 60%. For each scenario, 50,000 trials were simulated.

The operating characteristics under several scenarios of true ORRs of FGF19 positive and negative patients are shown in Table 10-5 and Table 10-6.

Under the scenario 1 (the percentages of FGF19 positive and FGF19 negative patients enrolled in the Stage 1 are 20% and 80%),

- If the true ORR in both FGF19 positive and negative patients is 40%, the probability to stop at Stage 1 for efficacy in unselected population is 0.889.
- If the true ORR in FGF19 positive and negative patients is 10%, probabilities to stop enrollment early for futility are 0.600 (FGF19 positive group) and 0.564 (FGF19 negative group), and the probability to show efficacy in either unselected or at least one subgroup is 0.004.
- If the true ORRs in FGF19 positive and negative patients are 10% and 40% respectively, the probability to stop enrollment early for efficacy is 0.685, and the probability to stop enrollment early for futility in FGF19 positive group is 0.232.
- If the true ORRs in FGF19 positive and negative patients are 40% and 10% respectively, the probability to stop enrollment early for efficacy is 0.017, and probability to show efficacy in either unselected of at least one subgroup is 0.796.

[redacted]

Table 10-5 Operating Characteristics (scenario 1: the percentages of FGF19 positive and FGF19 negative patients enrolled in the Stage 1 are 20% and 80%)

True ORR		Probability to stop study for success* at Stage 1	Probability to stop subgroup enrollment for futility** at Stage 1		Probability to show clinically relevant efficacy* at final analysis***		Overall probability to show clinically relevant efficacy* in either unselected, or at least one subgroup
$FGF19^+$	$FGF19^-$		$FGF19^+$	$FGF19^-$	$FGF19^+$	$FGF19^-$	
5%	5%	0.000	0.889	1.000	0.000	0.176	0.000
5%	10%	0.000	0.888	0.994	0.000	0.316	0.002
5%	20%	0.026	0.869	0.850	0.000	0.640	0.105
5%	30%	0.241	0.693	0.450	0.000	0.801	0.488
5%	40%	0.643	0.336	0.125	0.001	0.886	0.849
10%	5%	0.000	0.765	1.000	0.007	0.250	0.002
10%	10%	0.000	0.761	0.994	0.009	0.317	0.004
10%	20%	0.039	0.743	0.847	0.007	0.635	0.113
10%	30%	0.289	0.579	0.443	0.007	0.787	0.500
10%	40%	0.685	0.274	0.120	0.003	0.876	0.856
20%	5%	0.000	0.501	1.000	0.181	0.111	0.090
20%	10%	0.002	0.502	0.993	0.178	0.271	0.091
20%	20%	0.074	0.489	0.835	0.169	0.598	0.200
20%	30%	0.387	0.368	0.421	0.154	0.757	0.566
20%	40%	0.768	0.162	0.108	0.142	0.853	0.881
30%	5%	0.000	0.294	1.000	0.581	0.154	0.410
30%	10%	0.006	0.292	0.990	0.580	0.298	0.415
30%	20%	0.128	0.283	0.808	0.567	0.572	0.491
30%	30%	0.490	0.206	0.387	0.536	0.730	0.727
30%	40%	0.835	0.085	0.093	0.511	0.836	0.928
30%	5%	0.000	0.294	1.000	0.581	0.154	0.410
40%	5%	0.002	0.151	0.998	0.886	0.000	0.752
40%	10%	0.017	0.150	0.980	0.883	0.264	0.753
40%	20%	0.201	0.144	0.758	0.873	0.564	0.785
40%	30%	0.590	0.101	0.337	0.857	0.715	0.886
40%	40%	0.889	0.039	0.073	0.844	0.815	0.971

* show the posterior probability of ORR included in [0, 0.15) is less than 0.10 and the posterior median ORR is 0.30 or more

** show the posterior probability of ORR in a FGF19-based subgroup being included in [0, 0.15) is more than 0.80

*** conditional probability to show clinically relevant efficacy and move to Stage 2 without stop study for success or futility at Stage 1

Under the scenario 2 (the percentages of FGF19 positive and FGF19 negative patients enrolled in the Stage 1 are 40% and 60%),

- If the true ORR in both FGF19 positive and negative patients is 40%, the probability to stop at Stage 1 for efficacy in unselected population is 0.889.
- If the true ORR in FGF19 positive and negative patients is 10%, probabilities to stop enrollment early for futility are 0.817 (FGF19 positive group) and 0.940 (FGF19 negative

[redacted]

group), and probability to show efficacy in either unselected or at least one subgroup is 0.004.

- If the true ORRs in FGF19 positive and negative patients are 10% and 40% respectively, the probability to stop enrollment early for efficacy is 0.386, and the probability to stop enrollment early for futility in FGF19 positive group is 0.553.
- If the true ORRs in FGF19 positive and negative patients are 40% and 10% respectively, the probability to stop enrollment early for efficacy is 0.126, and probability to show efficacy in either unselected or at least one subgroup is 0.829.

Table 10-6 Operating Characteristics (scenario 2: the percentages of FGF19 positive and FGF19 negative patients enrolled in the Stage 1 are 40% and 60%)

True ORR		Probability to stop study for success* at Stage 1	Probability to stop subgroup enrollment for futility** at Stage 1		Probability to show clinically relevant efficacy* at final analysis***		Overall probability to show clinically relevant efficacy* in either unselected, or at least one subgroup
$FGF19^+$	$FGF19^-$		$FGF19^+$	$FGF19^-$	$FGF19^+$	$FGF19^-$	
5%	5%	0.000	0.980	0.997	0.000	0.004	0.000
5%	10%	0.000	0.980	0.968	0.001	0.060	0.002
5%	20%	0.006	0.976	0.724	0.001	0.350	0.101
5%	30%	0.076	0.910	0.346	0.001	0.670	0.463
5%	40%	0.287	0.707	0.105	0.000	0.879	0.822
10%	5%	0.000	0.909	0.997	0.019	0.008	0.002
10%	10%	0.000	0.909	0.967	0.021	0.051	0.004
10%	20%	0.018	0.901	0.719	0.019	0.333	0.107
10%	30%	0.128	0.817	0.346	0.015	0.648	0.470
10%	40%	0.385	0.592	0.104	0.010	0.860	0.825
20%	5%	0.001	0.629	0.996	0.250	0.000	0.094
20%	10%	0.006	0.628	0.965	0.245	0.051	0.097
20%	20%	0.075	0.613	0.710	0.224	0.297	0.206
20%	30%	0.286	0.527	0.337	0.200	0.602	0.545
20%	40%	0.591	0.337	0.097	0.181	0.825	0.857
30%	5%	0.011	0.315	0.988	0.635	0.000	0.439
30%	10%	0.039	0.320	0.939	0.625	0.052	0.441
30%	20%	0.201	0.306	0.658	0.587	0.263	0.521
30%	30%	0.489	0.248	0.290	0.553	0.544	0.737
30%	40%	0.767	0.145	0.078	0.500	0.782	0.920
40%	5%	0.055	0.119	0.944	0.894	0.000	0.793
40%	10%	0.130	0.118	0.857	0.890	0.031	0.800
40%	20%	0.388	0.115	0.538	0.861	0.238	0.827
40%	30%	0.686	0.086	0.216	0.830	0.507	0.908
40%	40%	0.886	0.047	0.054	0.810	0.748	0.972

* show the posterior probability of ORR included in [0, 0.15) is less than 0.10 and the posterior median ORR is 0.30 or more

** show the posterior probability of ORR in a FGF19-based subgroup being included in [0, 0.15) is more than 0.80

*** conditional probability to show clinically relevant efficacy and move to Stage 2 without stop study for success or futility at Stage 1

[redacted]

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent if applicable: or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

[For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that

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in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e. LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation

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checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1 – Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

Document type:	TA Specific Guideline
Document status:	Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
Release date:	29-Nov-2011
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

[redacted]

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

[redacted]

- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

[redacted]

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

[redacted]

and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.1.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately

[redacted]

for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.1.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However,

[redacted]

in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
  - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
  - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
  - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[redacted]

Response Criteria	Evaluation of non-target lesions

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

[redacted]

14.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.1.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

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

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative

[redacted]

cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of

[redacted]

response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control,

[redacted]

patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.1.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

[redacted]

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

[redacted]

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

[redacted]

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

Date of discontinuation is the date of the end of treatment visit.

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

[redacted]

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.1.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.1.25
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

[redacted]

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision

[redacted]

- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.1.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response

[redacted]

at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

[redacted]

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

14.1.40 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

[redacted]

14.2 Appendix 2 – Child-Pugh classification of severity of liver disease

Child-Pugh classification system

The CPC is used to assess the severity of impaired hepatic function in patients with liver cirrhosis (Child 1964, FDA guidance 2003). In general, it is used to determine the risk to a patient with regard to the treatment(s) (e.g. surgery, transplant, medication), and, to suggest the perceived survival of the patient over a period of time.

Hepatocellular carcinoma patients who have Child-Pugh grade A score (5 - 6 points) at the baseline screening are eligible for participating in Study CFGF401X2101, provided that the patients meet all other eligibility criteria, see Section 5.

Calculation and interpretation for Child-Pugh scores

The severity of liver disease is based on the CPC criteria, which will be calculated based on clinical findings and laboratory results during the screening period. Five variables are considered (severity of ascites, hepatic encephalopathy, abnormality in serum bilirubin, serum albumin and clotting times). A score (between 1 and 3) is accordingly assigned to each of these factors (Table 14-6). The sum of the scores provides the Child-Pugh score, which corresponds to a Child-Pugh grade (or Child's grade) of A, B or C (Table 14-7).

Table 14-6 Child-Pugh score calculation

	Points assigned			
Variables	**1**	**2**	**3**	**Units**
Total Bilirubin	< 2 (< 34)	2-3 (34-50)	> 3 (> 50)	mg/dL (µmol/L)
Serum Albumin	> 35 (> 3.5)	28-35 (2.8-3.5)	< 28 (< 2.8)	g/L (g/dL)
PT (or INR)	< 4 (< 1.7)	4-6 (1.7-2.30)	> 6 (> 2.30)	sec (no unit)
Ascites	Absent	Slight	Moderate	no unit
Hepatic Encephalopathy*	None	Grade 1-2	Grade 3-4	no unit

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
*Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
*Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
*Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
*Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Table 14-7 Child-Pugh score interpretation

Severity (grade)	Child-Pugh Score
A	5 - 6
B	7 - 9
C	10 - 15

References (available upon request)

Child CG, Turcotte JG (1964). Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders:50-64

FDA Guidance for industry (2003). pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling

[redacted]

14.3 Appendix 3 – Hepatocellular carcinoma staging systems

Staging systems

Clinical staging is crucial for risk stratification during cancer management. For HCC, a number of clinical staging systems have been developed mainly from HCC patients of different etiologies and extent of disease. The BCLC system is most widely studied and will be assessed at screening for all patients participating in this study:

For more information on patient eligibility, please refer to the core text of the study protocol.

Barcelona-Clinic Liver Cancer system

The BCLC staging system (Table 14-8) was developed based on the combination of data from several independent studies representing different disease stages and/or treatment modalities. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms (Llovet et al 2008).

Table 14-8 Barcelona-Clinic Liver Cancer system

BCLC stage	PS	Tumor Features	Liver Function
Stage A* (early HCC)			
A1	0	Single < 5 cm	No portal HTN** and normal bilirubin
A2	0	Single < 5 cm	Portal HTN, normal bilirubin
A3	0	Single < 5 cm	Portal HTN, abnormal bilirubin
A4	0	Up to 3 tumors < 3 cm	Child-Pugh class A - B
Stage B (intermediate HCC)	0	Large multinodular	Child-Pugh class A - B
Stage C (advanced HCC)	1 - 2	Vascular invasion or extrahepatic spread	Child-Pugh class A - B
Stage D (end-stage HCC)	3 - 4	Any of the above	Child-Pugh class C

* Stages A1, A2, A3 and A4 will be considered “Stage A” for data collection.
** HTN = Hypertension

Only BCLC Stage C HCC patients are eligible for participating in this study, provided that the patients meet all other eligibility criteria, see Section 5.

References (available upon request)

Llovet, J. M., et al. "Sorafenib in advanced hepatocellular carcinoma." N.Engl.J.Med. 359.4 (2008): 378-90.

[redacted]

14.4 Appendix 4 – Prohibited concomitant medications and permitted concomitant medications requiring caution

Table 14-9 Prohibited concomitant medications

Mechanism of Interaction	Drug Name
Known BSEP inhibitors	Atorvastatin, cerivastatin, cyclosporine , glyburide, reserpine, rifampicin, troglitazone, valinomycin
CYP1A2 substrate with NTI	Theophylline, tizanidine
CYP2C9 substrate with NTI	Phenytoin, warfarin
CYP3A4/5 substrate with NTI	Quinidine, [terfenadine], astemizole, cyclosporine, sirolimus, tacrolimus, pimozide, alfentanil, fentanyl, diergotamine, ergotamine, cisapride, thioridazine, dihydroergotamine

Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interactions (DDI) and Co-medication considerations (release date: Apr 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database
Dawson S et al, Drug Met Dispos, 2012, 40 :130-138
Morgan et al, Tox Sci, 2013, 136: 216-241
NTI: narrow therapeutic index

Table 14-10 Permitted concomitant medications requiring caution

Mechanism of Interaction	Drug Name
Strong CYP3A4/5 inhibitor	Clarithromycin, troleandomycin, indinavir, itraconazole, posaconazole, voriconazole, boceprevir, telaprevir, cobicistat, conivaptan, mibefradil, grapefruit juice, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, sequinavir/ritonavir, telithromycin, indinavir/ritonavir, tipranoavir/ritonavir, danoprevir/ritonavir, eltegravir/ritonavir
Strong CYP3A4/5 inducer	Avasimibe, carbamazepine, mitotane, phenobarbital, rifabutin, St. John's wort, rifampin, enzalutamide
Potential BSEP inhibitors	Benzbromarone, everolimus, fenofibrate, fusidic acid, indinavir, lopinavir, nelfinavir, olmesartan, sitaxsentan, tolcapone
MRP2/3/4 and/or NTCP and/or OATP1B1/3 inhibitors	Atazanavir, bendroflumethiazide, clarithromycin, clofazimine, clotrimazole, doxazosin, entacapone, epalrestat, ezetimibe, febuxostat, gemfibrozil, indomethacin, lopinavir, losartan, lovastatin, nelfinavir, nifedipine, olmesartan, repaglinide, rifaximin, rilpivirine, sildenafil, simvastatin, telmisartan, tranilast, valsartan

Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interactions (DDI) and Co-medication considerations (release date: Apr2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database
Dawson S et al, Drug Met Dispos, 2012, 40 :130-138
Dong Z et al, Mol Pharmaceutics, 2013, 10 :1008-1019
Kalliokoski A and Niemi M, Br J Pharmacol, 2009, 158 :693-705
Morgan et al, Tox Sci, 2013, 136: 216-241

14.5 Appendix 5 – Guidelines for management of diarrhea

Patients should receive clear instructions regarding the possibility of experiencing diarrhea and the necessity to contact the treating physician. As bile acid-induced diarrhea is a predictable

effect of the trial drug, patients experiencing diarrhea ≥ grade 1 should be treated with cholestyramine (also named as colestyramine), 4 g daily initially, following local prescribing guidance.

It is recommended that patients initially take cholestyramine at bed time and if needed for further control of diarrhea take an extra dose of cholestyramine in the afternoon (e.g. 3-4 pm) and/or late morning (e.g. 11 am). Other drugs need to be administered at least 1 hour before or 4 hours after cholestyramine administration.

The maximum recommended daily dose is six packets or scoopfuls of cholestyramine (4 g/dose) for oral suspension (24 g anhydrous cholestyramine resin), and according to the local prescribing document. Although the recommended dosing schedule is maximal 1 to 4 doses daily, cholestyramine for oral suspension may be administered in 1 to 6 doses per day. Cholestyramine should not be taken in its dry form and should be mixed with water or other juices before ingesting.

Patients need to be alerted to the possibility of symptoms of bloating, and should consider reducing the dose to 2 g if these symptoms are more severe than the diarrhea.

It is recommended that increases in dose be gradual, such as 2 – 4 g every 3 days. Other treatment of diarrhea and complications (e.g. repletion of electrolytes) should follow local guidance.

Because cholestyramine binds bile acids, long-term treatment with cholestyramine may interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E and K. Monitor of vitamins, including vitamin K, should be done according to the local clinical guidelines. When cholestyramine is given for long periods of time, concomitant supplementation with water-miscible (or parenteral) forms of fat-soluble vitamins should be considered. If cholestyramine is poorly tolerated loperamide should be considered, initially 4–8 mg daily and a maximum of 16 mg daily.

Table 14-11 Criteria for interruption and re-initiation of FGF401 treatment for diarrhea management

Worst toxicity[a]	Recommended dose modifications any time during a cycle of therapy (including intended day of dosing)[c, d]
Grade 1	Maintain dose level, then: If resolved to normal within 24 hours, then no need to prescribe colestyramine If Grade 1 is persistent after 24 hours, then colestyramine should be considered based on investigator's decision
Grade 2	Maintain dose level and start colestyramine immediately, then: 1. If resolved to ≤ Grade 1 within 24 hours after colestyramine administered, then colestyramine should be kept based on investigator's decision 2. If Grade 2 is persistent after 24 hours of colestyramine administered, then continuously administer colestyramine for another 6 days and by then: a. If resolved to ≤ Grade 1, maintain dose level and keep using colestyramine b. If Grade 2 is persistent, then ↓ 1 dose level and keep using colestyramine

[redacted]

Worst toxicity[a]	Recommended dose modifications any time during a cycle of therapy (including intended day of dosing)[c, d]
Grade 3[b]	Maintain dose level and start colestyramine immediately, then: 1. If resolved to ≤ Grade 1 within 24 hours after colestyramine administered, then keep using colestyramine 2. If resolved to Grade 2 by 24 hours of colestyramine administered, then continuously administer colestyramine for another 6 days and by then: a. If resolved to ≤ Grade 1, maintain dose level and keep using colestyramine b. If Grade 2 is persistent, then ↓ 1 dose level and keep using colestyramine If Grade 3 is persistent after 24 hours of colestyramine administered, then omit dose and continuously administer colestyramine for another 6 days, by then: a. If resolved to ≤ Grade 1, then ↓ 1 dose level and keep using colestyramine b. If ≥ Grade 2 is persistent, then discontinue patient from study drug treatment
Grade 4[b]	Omit dose and start colestyramine immediately, then: 1. If resolved to ≤ Grade 1 within 7 days after colestyramine administered, then ↓ 1 dose level and keep using colestyramine 2. If not resolved to ≤ Grade 1 within 7 days after colestyramine administered, then discontinue patient from study drug treatment

[a] CTCAE version 4.03 will be used for all grading.
[b] For Grade 3 and 4 diarrhea, the supportive measurement should be implemented based on local clinical guidance
[c] For any ≥ Grade 2 diarrhea with multiple occurrences, investigator should discuss with Novartis for any opportunity to change dosing schedule or further dose reductions.
[d] In any circumstance if patient needs to be discontinued from study drug treatment due to diarrhea, investigator should discuss with Novartis for any opportunity to change dosing schedule or further dose reductions.

14.6 Appendix 6 - Guidelines for management of hyperphosphatemia

Hyperphosphatemia is a disorder characterized by laboratory test results that indicate an elevation in the concentration of inorganic phosphorus in blood. Clinical judgment and institutional standards in the management of hyperphosphatemia and the timing of stopping and/or re-initiating FGF401 treatment as a function of phosphate levels will be left to the discretion of the treating physician. Differences in phosphate management will not be considered as protocol deviations. Please refer to the Sevelamer Package Insert for additional information.

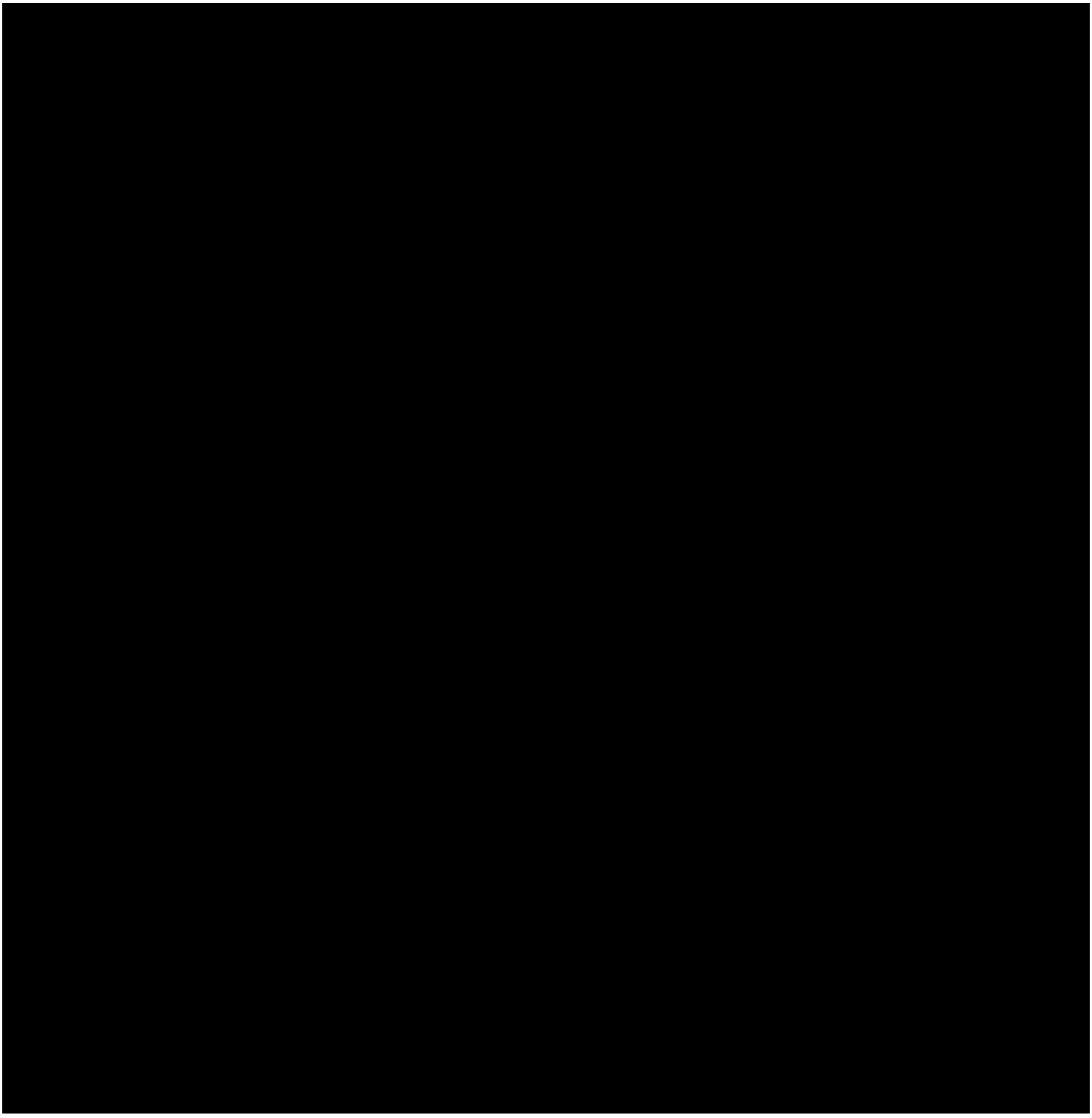
Table 14-12 Criteria for for interruption and re-initiation of FGF401 treatment for hyperphosphatemia management

Serum inorganic phosphorus (Pi) value	Recommended Dose Modifications any time during a cycle of therapy
Serum Pi > 5.5 – 7.0 mg/dL	Maintain dose level and start phosphorus lowering therapy: Sevelamer dose should be adjusted based on the serum phosphorus level with the goal of maintaining ≤ 7.0 mg/dL. Refer to Package Insert of Sevelamer for dosing guidelines.

[redacted]

Serum inorganic phosphorus (Pi) value	**Recommended Dose Modifications any time during a cycle of therapy**
Serum Pi > 7.0 mg/dL lasting more than 7 days despite maximal dosing of Sevelamer or Confirmed single serum phosphorus > 9.0 mg/dL regardless of Sevelamer dose	Omit dose until resolved to serum Pi ≤ 7.0 mg/dL, then: ● Continue Sevelamer and adjust the Sevelamer dose with the goal of maintaining serum phosphorus ≤ 7.0 mg/dL. Hold Sevelamer once serum phosphorus is ≤ 5.5 mg/dL ● If serum phosphorus is resolved to ≤ 7.0 mg/dL within 14 days of suspending FGF401, then resume FGF401 at the same dose level ● If serum phosphorus is not ≤ 7.0 mg/dL within 14 days of suspending FGF401 despite maximal dosing of Sevelamer, discontinue patient from the study drug treatment ● All patients will continue to be followed-up until resolution to serum phosphorus ≤ 7.0 mg/dL If hyperphosphatemia recurs and requires another FGF401 dose interruption: FGF401 dose should be restarted based on above criteria at ↓ 1 dose level. Further dose reductions of FGF401 may be taken as needed, but should first be discussed with Novartis.
Serum phosphorus > 10.0 mg/dL	Discontinue patient from the study

[redacted]



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14.8 Appendix 8 – Test meal guidelines

During the food effect portion of the study, food intake should be supervised on days of PK profiles collection. Patients on food effect cohort will consume a low-fat, light breakfast and then will receive the treatment with FGF401. The meal should be consumed within 30 minutes. FGF401 will be administered with one glass of water. No food will be allowed for at least 4 hours post-dose. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Note: For the fed conditions, the meal should be consumed within 30 minutes. If > 30 minutes is required to complete the meal, then FGF401 should be administered relative to the end of the meal.

Recommendations for sample test meals are outlined in Table 14-14. Alternative meals with equivalent nutritional content may be used.

[redacted]

Table 14-14 Test meal examples

Low-fat Breakfast (approximately 500 calories and 20 grams of fat)
6 ounces of orange juice (except Seville) 8 ounces of 2% milk 1 banana ¾ cups of cereal 1 slice of toast 2 teaspoons of butter
Coffee, tea, or grapefruit juice is not permitted as part of either test meal. Water is allowed during the test meal.

A registered dietician at the research site should determine the appropriate meal to be consumed, based on the fat and calorie requirements assigned to the patient for that treatment day. The start/stop time of meal consumption, and estimated % of test meal consumed (based on fat and caloric content), must be listed in the Meal Record eCRF for patients allocated in exploratory food effect cohort.

14.9 Appendix 9- Guidelines for immune-related Response Criteria (irRC) using one-dimensional measurements (simulating RECIST 1.1)

14.9.1 Introduction

The currently used immune-related response criteria (irRC) uses unidimensional measurements to assess tumor response and it is an adaptation of the original irRC published by Wolchok (Wolchok 2009, Nishino 2013).

The purpose of this document is to summarize the irRC guidelines in details focusing on differences in tumor response assessments between irRC and RECIST v1.1.

The primary difference between irRC and RECIST 1.1 is the definition of progressive disease. The definitions of baseline target/non target lesions, number of lesions selected at baseline, the criteria for lesion measurement method of evaluation of response and definition of response are the same for irRC and RECIST 1.1 and are available in the RECIST 1.1 guidelines (Appendix 1).

14.9.2 New lesions and non-target lesions

In irRC a new lesion does not automatically indicate progressive disease.

New measurable lesions are added to the sum of diameters of the previously existing target lesions, and the sum of diameters is followed at each subsequent tumor assessment.

New measureable lesions are defined using the same criteria as for baseline target lesions in RECIST v1.1. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions up to 10 lesions in total.

Non-target lesions (baseline and new non-measurable lesions) are used primarily for determination of Complete Response (CR). The RECIST v1.1 definitions for the assessment of non-target lesions apply. A CR requires that all non-target lesions disappear (both those present

[redacted]

at baseline and any new non-measurable lesions that have appeared during the study). If after worsening a non-target lesion becomes measurable, it should still be followed as a non-target lesion. Worsening of non-target lesions and new non-measurable lesions only indicate disease progression if there is unequivocal evidence of disease progression (Table 14-15).

14.9.3 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions is calculated (at baseline and throughout the study). The diameters of any new measurable lesions are included in the sum of diameters at each assessment to provide the total tumor burden. At each assessment, percent change in the sum of diameters is calculated and compared to baseline or to nadir in order to evaluate the target lesion response (including new measurable lesions) (Section 14.9.4). This evaluation combined with the status of non-target lesions (baseline and new non-measurable lesions) is then used to determinate the overall lesion response (Table 14-15). The thresholds for irPR and irPD assessment are the same as for RECIST v1.1.

14.9.4 Definitions of response categories and evaluation of overall lesion response

In irRC, the overall response is primarily based on target lesions (baseline and new measurable lesions). The non-target lesions only contribute to define irCR, and irPD in the case of unequivocal progression, as shown below in Table 14-15.

Like in RECIST 1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. Unlike RECIST 1.1, irPD also requires confirmation at a new assessment after at least 4 weeks.

The response categories are defined as follows:

- Immune related Complete Response (irCR): Disappearance of all non-nodal target lesions and non-target lesions in two consecutive observations not less than 4 weeks apart. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. (Sum of diameters may be greater than zero at the time of CR, if nodal lesions are included as target lesions).
- Immune related Partial Response (irPR): At least a 30% decrease in the sum of diameters of all target lesions including new measurable lesions in two consecutive observations not less than 4 weeks apart, taking as reference the baseline sum of diameters.
- Immune related Progressive Disease (irPD): At least a 20% increase in the sum of diameters of all measured target lesions including new measurable lesions. The irPD must be confirmed in a second evaluation not less than 4 weeks later, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Worsening of non-target lesions (existing or new) only indicate PD when there is unequivocal evidence of progression, confirmed in a second evaluation not less than 4 weeks later.
- Immune related Stable Disease (irSD): Neither a sufficient shrinkage to qualify for irPR or irCR, nor an increase in lesions which would qualify for irPD.

[redacted]

- Unknown (UNK): Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a method significantly different from baseline that prevents reasonable comparison to the prior assessments.

Table 14-15 Overall response at each assessment

Target and new measurable lesions (Tumor burden), * (%)	Non-target lesions (both baseline and new non-measurable)	Overall lesion response
-100	Absent	irCR[a]
-100	Stable/not evaluated	irPR[a]
≤ -30	Absent/Stable/not evaluated	irPR[a]
> -30 and <+20	Absent/Stable/not evaluated	irSD
≥ +20	Any	irPD[a]
Any	Unequivocal progression	irPD[a]

* the diameter of new measurable lesions is included in the calculation of the sum of diameters

[a] to be confirmed after at least 4 weeks

14.9.5 References (available upon request)

Wolchok JD, Hoos A, O'Day S et al (2009). Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res; 15:7412-20.

Nishino M, Giobbie-Hurder A, Gargano M, et al (2013). Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res; 19:3936-3943.

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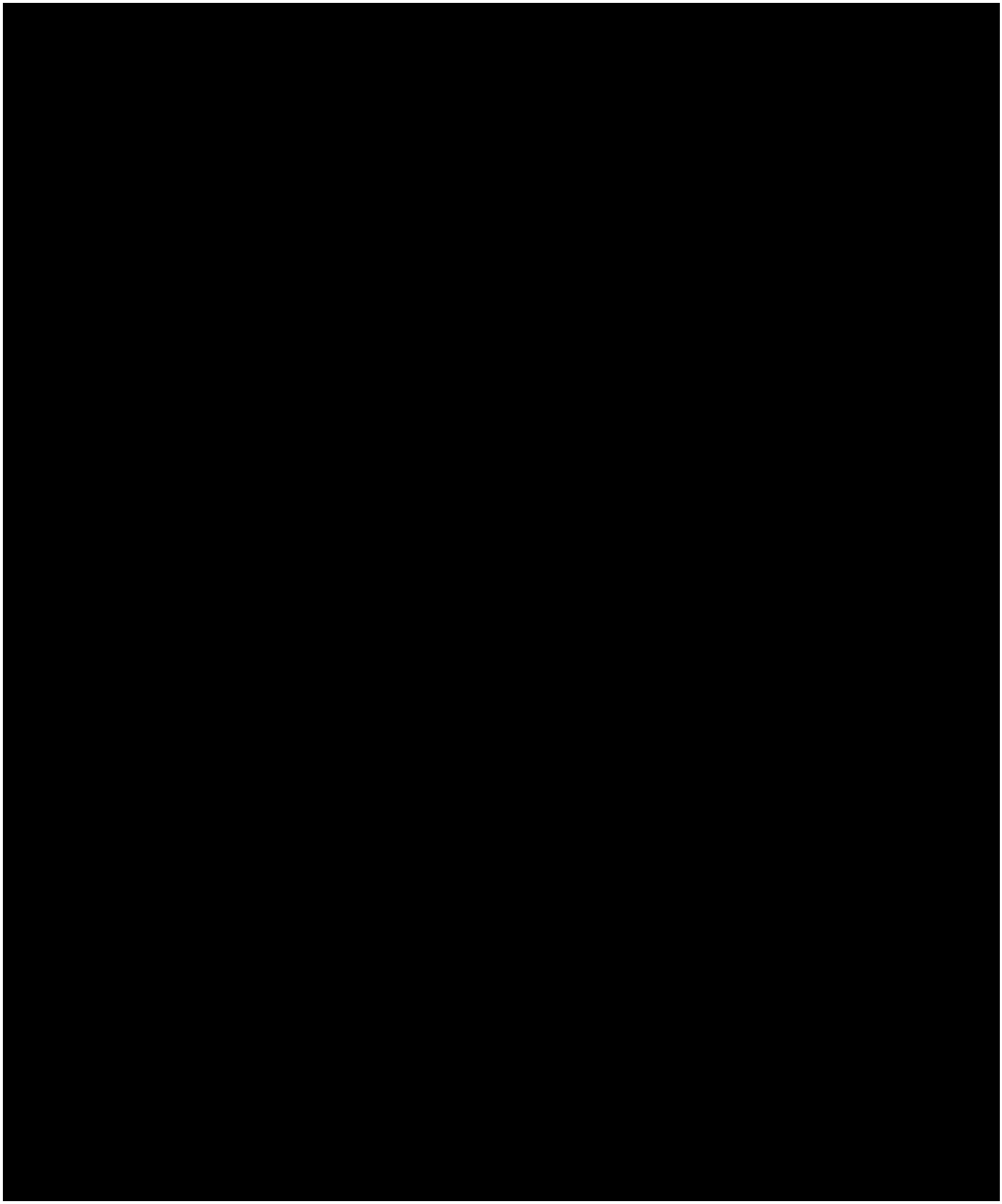

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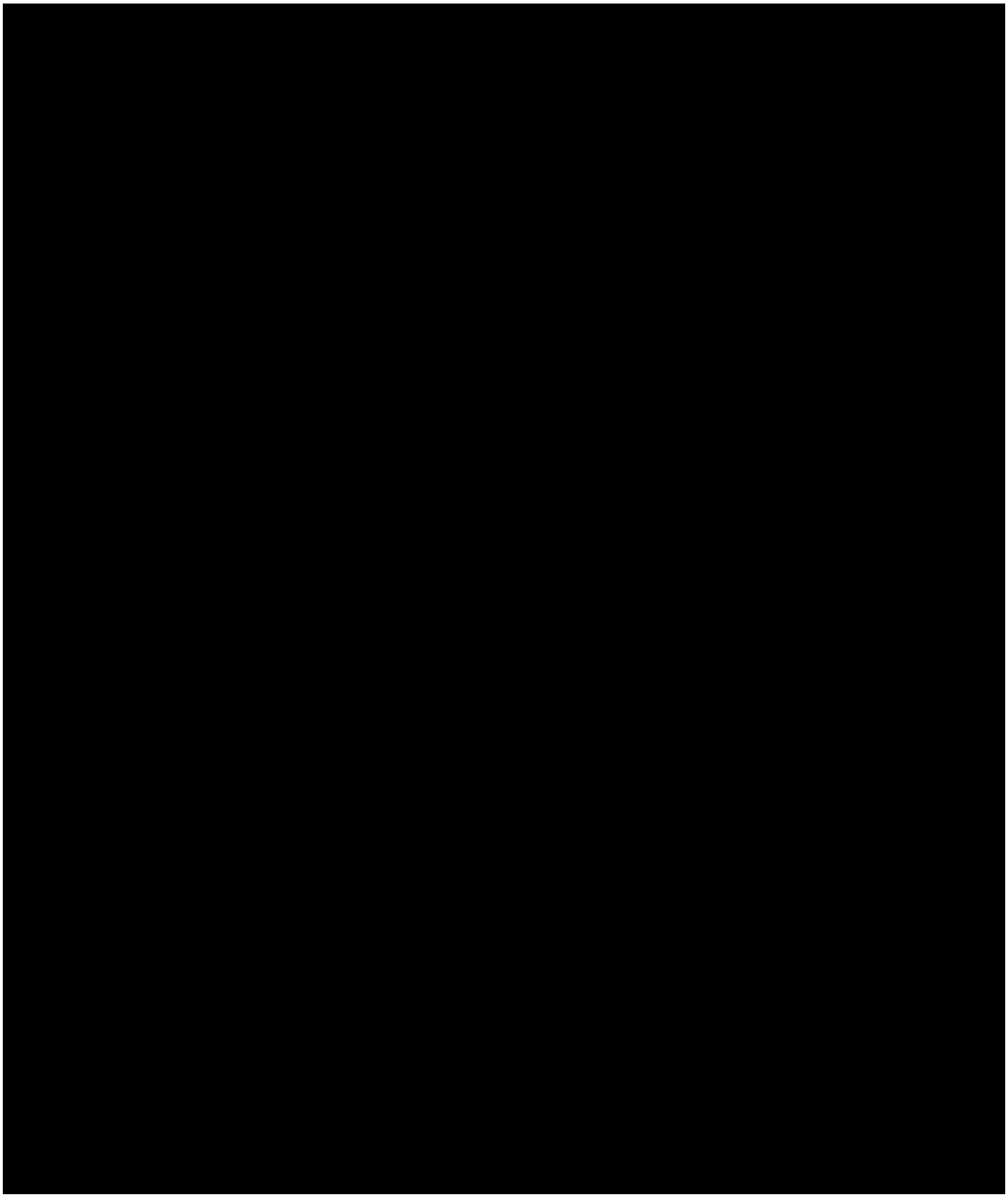

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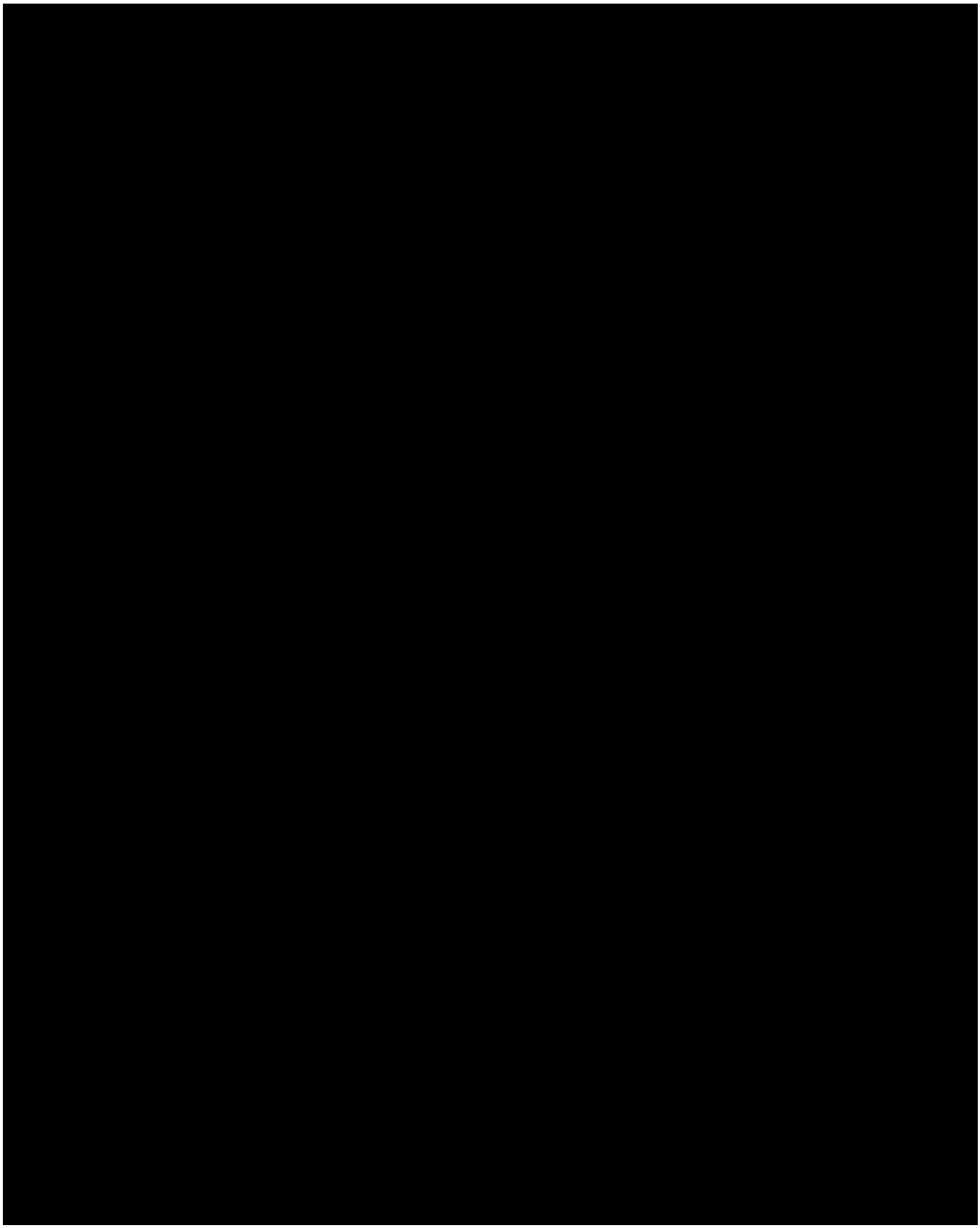

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14.11 Appendix 11- Recommended management algorithms for suspected toxicities

These guidelines for management of toxicities (Postow 2015) constitute guidance to the Investigator and are not intended to substitute institutional standard of care practice.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

[redacted]

14.11.1 GI adverse event management algorithm

GI Adverse Event Management Algorithm

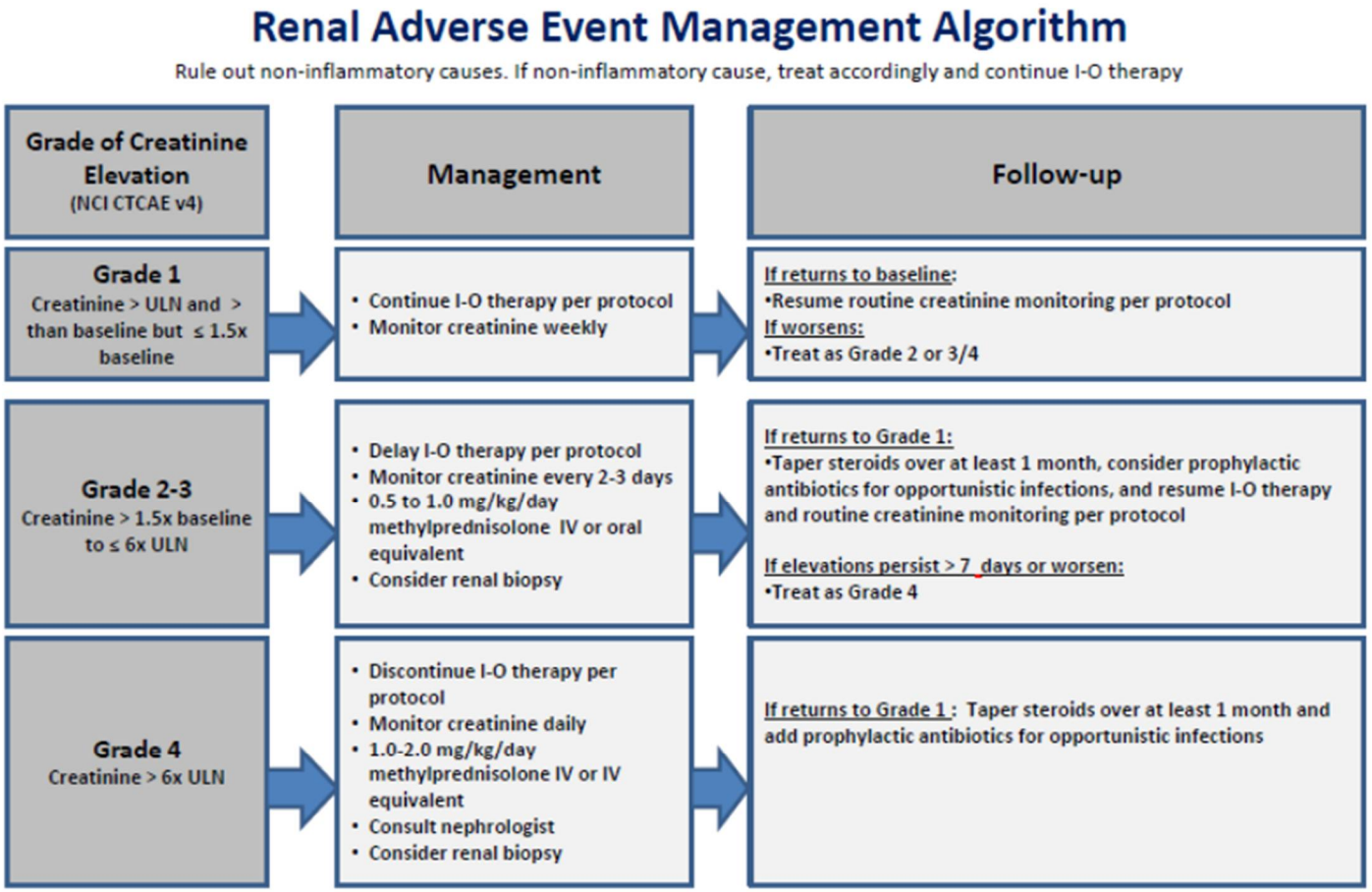
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

14.11.2 Renal adverse event management algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

14.11.3 Pulmonary adverse event management algorithm

Pulmonary Adverse Event Management Algorithm

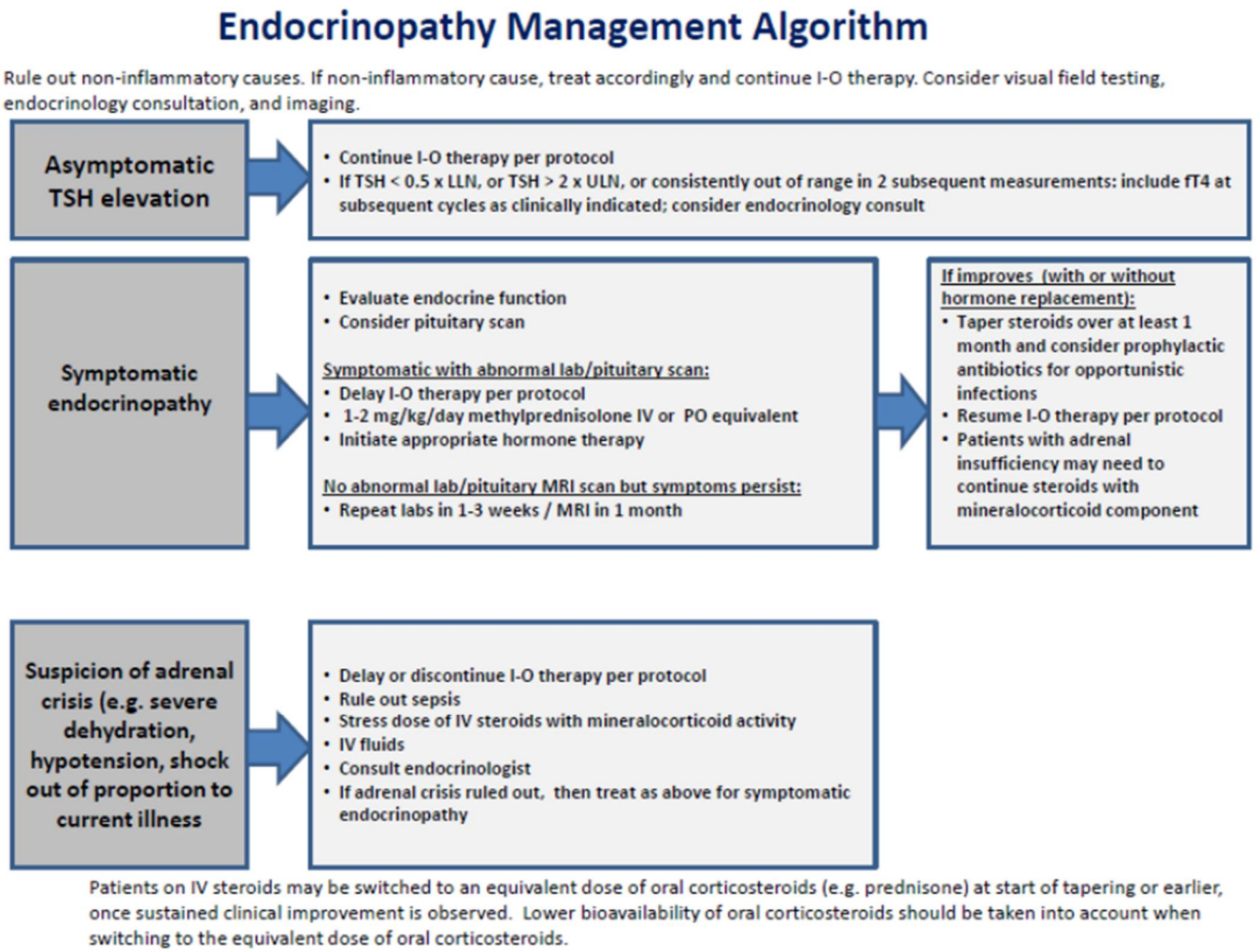
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

14.11.4 Endocrinopathy management algorithm



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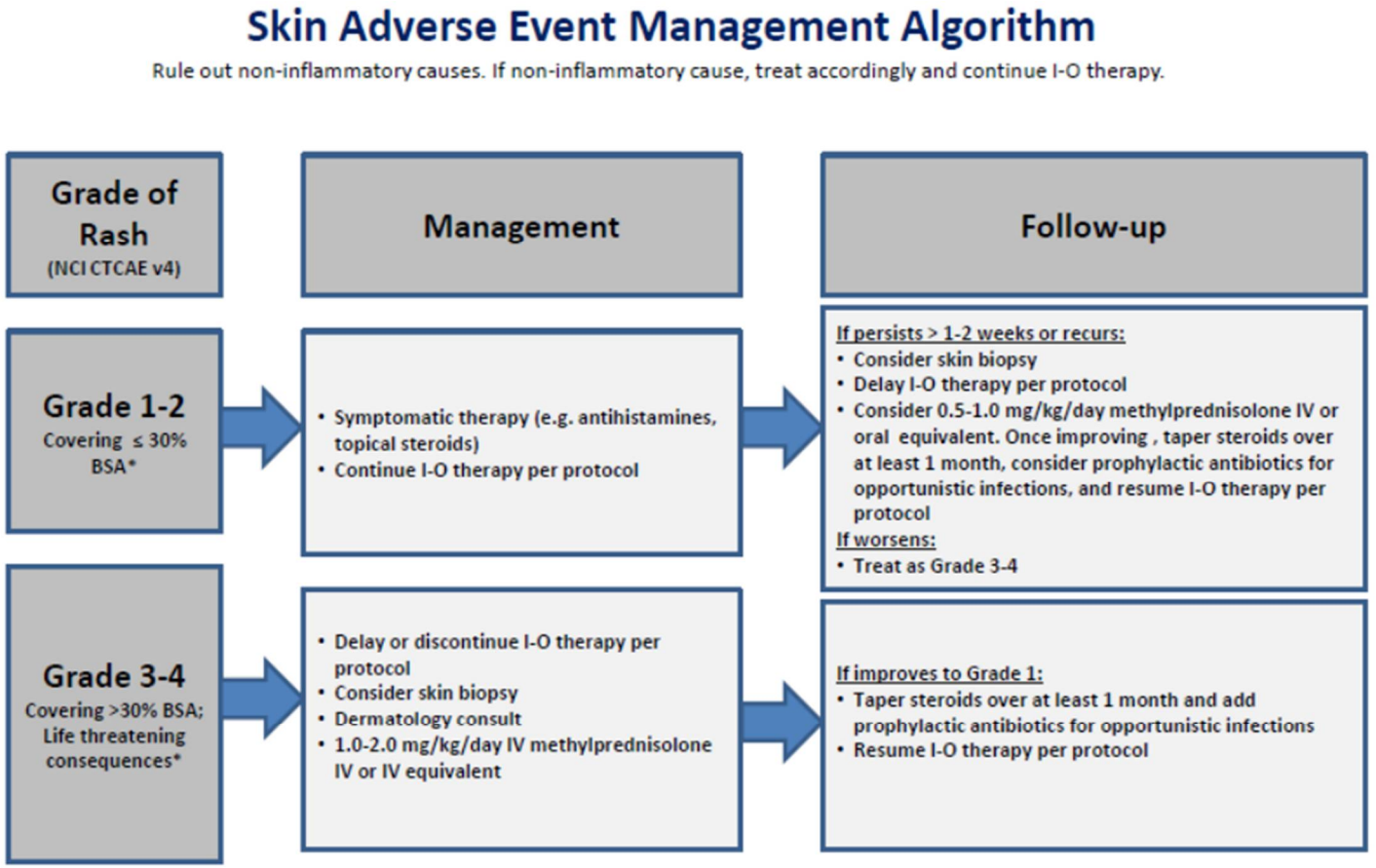
14.11.5 Skin adverse event management algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

[redacted]

14.11.6 Hepatic adverse event management algorithm

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

[redacted]

14.11.7 References (available upon request)

Postow MA, Chesney J, Pavlick AC, et al (2015). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med.;372(21):2006-17 (supplementary appendix).

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