NOVARTIS

Clinical Development

FGF401

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

Statistical Analysis Plan (SAP) for final CSR

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Nov-2018	Prior to DB lock	Amendment 1	Used the new template: SAP instead of RAP M3	All sections
			Added analysis plan for FGF401 in combination with PDR001	
			Removed all analysis plan related to the phase II part of the FGF+PDR001 combination because the phase II part of the FGF401+PDR001 combination will not start	
			Section 2.8.1: removed the definition of time to progression and added the definition of time to progression	section 2.8.1 section 2.8.1.1.1 section 2.8.2.2.3
			Section 2.8.1.1.1: added the description “pooled data of subjects who received the MTD/RP2D under fasted and fed conditions will be used”	
			Section 2.8.2.2.3: removed analyses for liver function parameters of interest	
26-Jun-2019	Prior to DB lock for final CSR	Amendment 1 for final CSR	Described rationale to not show Cmin	Section 2.8.4
			Added OS analysis at MTD/RP2D for the purpose of disclosure office	Section 2.8.1.1.1
			Added description that no specific summary tables or listing for AESIs will be provided	Section 2.8.2.1.2

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Subject-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CFGF401X2101 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on the Protocol Amendment 5.

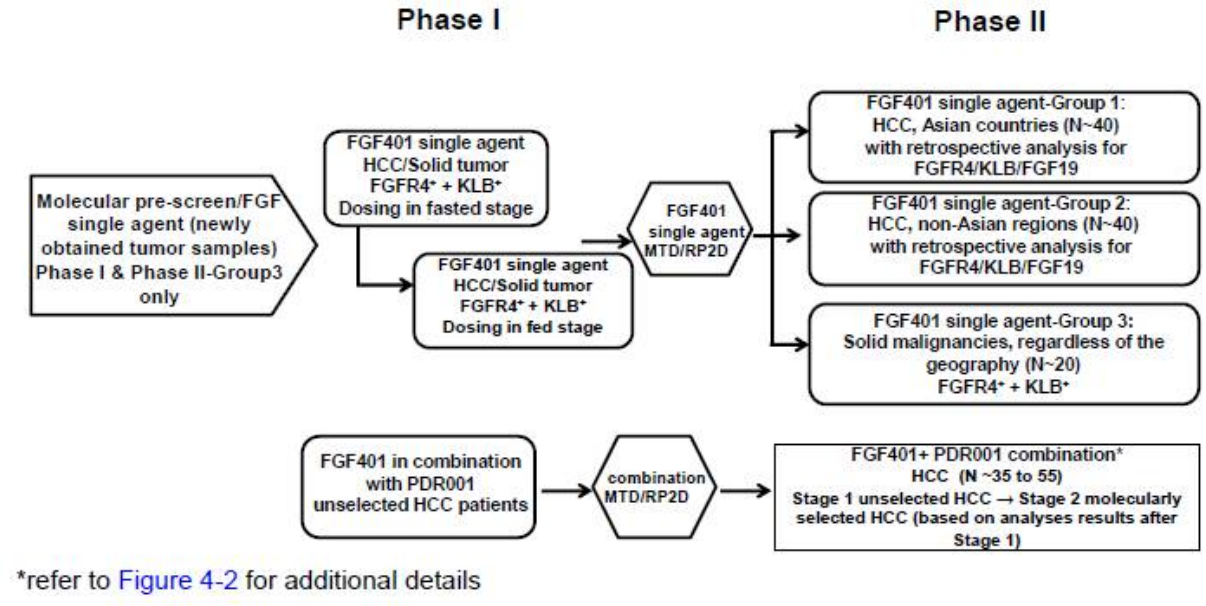
All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g. MTD/RDE declaration, IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

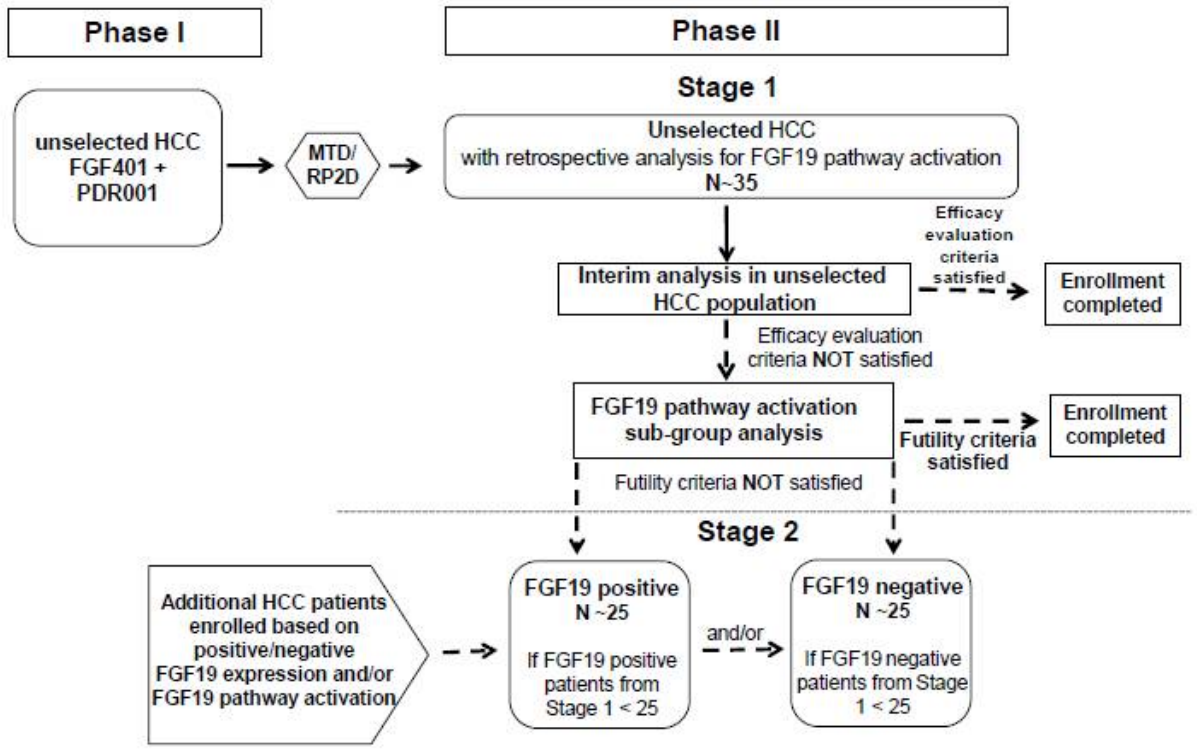
Figure 1-1 represents the study design for the single-agent part while figure 1-2 represents the same for the combination part. On Figure 1-2, the phase II has not been opened.

Figure 1-1 Study design



*refer to Figure 4-2 for additional details

Figure 1-2 Study design – FGF401 in combination with PDR001



1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
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 of FGF401 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
Secondary (Phase I and II part)	
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
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

Objective	Endpoint
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 Cmax, Cmin, AUCinf, AUClast, AUCtau and T1/2
To assess immunogenicity of PDR001	Presence and/or concentration of anti-PDR001 antibodies
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

2 Statistical methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS® version in the GPS environment. For analyses using R (version 3.0.2 and 3.2.3) and/or WinBUGS (version 14) /JAGS (version 4.1.0 and 4.2.0) (e.g. Bayesian analysis) in the MODESIM environment will be used. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 6.4 or above.

The study data will be analyzed and reported (in a primary CSR if final DBL has not occurred) based on all patients' data up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. The primary CSR will include all outputs planned within the TFL shells document. Additional data for patients continuing to receive study treatment past the data cutoff date of the primary CSR, as allowed by the protocol, will be reported once all patients have discontinued the study. However, only a selection of key outputs (indicated in the TFL shells document) for which additional data was collected will be provided for the final report.

Data from participating centers in this study protocol will be combined, so that an adequate number of Subjects will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and other

relevantmeasurements using descriptive statistics for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

A treatment is defined by the dose level, and food condition (fed or fasted, in FGF401 single agent phase I part only). During the phase I part of the single agent FGF401, cohorts of patients with the same treatment will be pooled into one single treatment group. Similarly, during the phase I part of the combination FGF401 + PDR001, cohorts of patients with the same combination treatment will be pooled into one single treatment group. Unless otherwise specified, data from the phase I and phase II parts, of any study arm, will not be pooled.

Unless otherwise specified, data will be summarized by part and treatment, within each study arm.

- Study part: phase I, phase II
- Study arm: FGF401 single agent, FGF401 in combination with PDR001

In addition, patients in FGF401 single agent phase II part will be analyzed according to the following 3 groups to which they were assigned.

- Group 1 (HCC patients from Asian countries)
- Group 2 (HCC patients from non-Asian countries)
- Group 3 (patients who have other solid tumors regardless of geography)

Because the enrollment of this study has been halted for business reason since 03Jul18 and the phase II part of the FGF401 in combination with PDR001 will not start, all analysis plan related to the phase II part of the FGF401 in combination with PDR001 arm are removed.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

FGF401 single agent:

Investigational drug will refer to FGF401. The terms investigational drug and study treatment are used interchangeably.

FGF401 in combination with PDR001:

Investigational treatment will refer to FGF401 + PDR001. The term investigational treatment may also be referred to as **study treatment**. For consistency across studies, the term study treatment will be used throughout this document.

2.1.1.2 Monotherapy vs combination studies

FGF401 single agent:

The expression ***monotherapy*** will be used to refer to investigational drug FGF401 the only component of the study treatment as defined in the study protocol.

FGF401 in combination with PDR001:

The expression ***combination therapy*** will be used to refer to the Investigational treatment FGF401 + PDR001, as defined in the protocol.

2.1.1.3 Date of first/last administration of study treatment

FGF401 single agent:

In the single agent arm, the date of first/ last administration of study treatment is derived as the first/last date when a non-zero dose of FGF401 was administered and recorded on the Dosage Administration Record (DAR) eCRF.

FGF401 in combination with PDR001:

The date of first administration of each component (FGF401, PDR001) is derived as the first date when a non-zero dose of each component was administered and recorded on the DAR eCRF. The date of last administration of FGF401 is the last date of administration of a non-zero dose of FGF401 was administered and recorded on the DAR eCRF. The date of last administration of PDR001 given Q3W is the last date of administration of a non-zero dose of PDR001 +20 days.

The date of first (last) administration of study treatment is derived as the first/last date of either FGF401 or PDR001 whichever earlier/ later respectively..

2.1.1.4 Study day

The study day **for safety assessments** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study day 1. Example: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is 5. For safety assessments before start of study treatment, the study day is negative and derived by (date of event – start date of study treatment). For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory abnormality is -3. Note, the day of start of study treatment is day 1, and the day before the date of first study treatment is day – 1, not day 0.

The study day for **other assessments** (e.g. efficacy, [redacted] etc.) will be calculated the same way as safey assessments.

2.1.1.5 Baseline

Baseline is the result of an investigation describing the “true” state of the before start of study treatment administration.

For **safety evaluations**, the last available assessment on or before the date of start of study treatment is taken as “Baseline” assessment. In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g. ECGs or vital signs), where study requires multiple replicates per

time point, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

For **efficacy assessments**, the last available assessment on or before the date of start of study treatment is taken as "baseline" assessment.

2.1.1.6 On-treatment assessment/event and observation periods

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

pre-treatment period: from day of patient's informed consent to the day before first administration of study treatment.

on-treatment period: from day of first administration of study treatment to 30 days after date of last administration of study treatment (including start and stop date)

post-treatment period: from 31 days after date of last administration of study treatment

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study treatment, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 30 days (for FGF401 single agent) or 150 days (for FGF401 in combination with PDR001). Following start of new antineoplastic therapy only treatment related adverse events will be collected. Select summaries of related adverse events and death will be produced for the combined on-treatment and post-treatment periods (Section 2.8.2.1).

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

2.2 Analysis Set/ Subject Classification/ Withdrawal of ICF/ Subgroups

2.2.1 Analysis sets

2.2.1.1 Full Analysis Set (FAS)

The full analysis set (FAS) comprises all patients who received at least one dose of study treatment. Patients enrolled in the phase I part will be analyzed according to the treatment they have been assigned to. Patients enrolled in the FGF401 single agent phase II part will be analyzed by Group. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

2.2.1.2 Safety Analysis Set (SS)

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

- The treatment assigned if it will be received at least once, or
- The first treatment received when starting therapy with study treatment if the assigned treatment will never be received.

Patients enrolled in the FGF401 single agent phase II part will be analyzed by Group.

2.2.1.3 Dose Determing Set (DDS)

The dose-determining analysis set (DDS) consists of all patients from the safety set in phase I part 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 $\geq$ 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 $\geq$ 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.

2.2.1.4 Per-Protocol Set (PPS)

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 SAP.

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 2.6). If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

2.2.1.5 PK analysis set

Pharmacokinetic analysis set (PAS)

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 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.

2.2.2 Subject Classification

Subjects may be excluded from the analysis populations defined above based on the protocol deviations (PD) entered in the database and/or on specific classification rules defined in Table 2-1.

Table 2-1 Classification based on PDs and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
Full analysis set	No written inform consent	Patient did not receive any dose of study treatment since day 1 of cycle 1 evaluation performed
Safety set	No written inform consent	Patient did not receive any dose of study treatment since day 1 of cycle 1 evaluation performed
Dose-determining set	No written inform consent	FGF401 single agent: Patient received less than 66% of the planned dose of FGF401 without having DLT in the first cycle of treatment in phase I part.

		Patient received at least 66% of the planned dose of FGF401 without having DLT but not received sufficient safety evaluation in the first cycle of treatment in phase I part Patient did not receive any dose of FGF401 since day 1 of cycle 1 evaluation performed FGF401 in combination with PDR001: Patient received less than 66% of the planned dose of FGF401 or not planned doses of PDR001 without having DLT in cycle 1 and cycle 2 of dosing. Patient received at least 66% of the planned dose of FGF401 and all planned doses of PDR001 without having DLT but not received sufficient safety evaluation in the first 2 cycles of treatment in phase I part Patient did not receive any dose of study treatment since day 1 of cycle 1 evaluation performed
Per-protocol set	No written inform consent No measurable lesion is present according to RECIST v1.1	Patient did not receive any dose of study treatment since day 1 of cycle 1 evaluation performed Patient had no appropriate tumor assessment post treatment
PK Analysis Set	No written inform consent	Patient did not receive any dose of study treatment since day 1 of cycle 1 evaluation performed Patient had no blood sample providing evaluable PK data

2.2.3 Withdrawal of Informed Consent

Any data collected in the clinical database after a Subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a Subject withdraws full consent is recorded in the eCRF.

[redacted]

2.3 Subject Disposition / Demographics /Other Baseline Characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.3.1 Subject disposition

The following will be tabulated:

- Number (%) of Subjects who are still on-treatment at the time of cut-off;
- Number (%) of Subjects who discontinued treatment and primary reasons for discontinuation;
- Number (%) of Subjects who discontinued from study and reasons for discontinuation;
- Number of (%) Subjects followed up after discontinuation of study treatment;

2.3.2 Demographic

Demographic data including age, sex, race, ethnicity, height, weight, body mass index, and ECOG performance status will be listed and summarized. In addition, following age categories will be summarized: 18- <65 years, 65- < 85 years, and ≥ 85 years.

BMI is calculated using the following formulas:

- BMI [kg/m2] = weight[kg] / (height[m]**2)

2.3.3 Medical History

A listing of medical history and current medical conditions will be provided, using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

2.3.4 Prior antineoplastic therapy

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

The number (%) of Subjects who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), setting at last treatment, best response at last treatment (defined to be the best response during the last treatment regimens recorded) and reason for discontinuation at last medication. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

Local HCC therapies will be listed.

2.3.5 Diagnosis and extent of cancer

The diagnosis and extent of cancer (disease history) will be listed. Prognistic factors for HCC will be summarized and listed.

2.4 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listing. The number (%) of Subjects with any CSR-reportable protocol deviation will be tabulated. The full list of protocol deviations is documented in the Study Specification Document (SSD).

2.5 Treatments (study treatment, concomitant therapies, compliance)

2.5.1 Study treatment

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) for each component of study treatment will be summarized. The duration of exposure will also be presented for the study treatment. Duration of exposure will be categorized into time intervals (≤6 weeks, >6-12 weeks, >12-18 weeks, >18-24 weeks, >24-52 weeks, >52 weeks); frequency counts and percentages will be presented for the number(%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment. See section 5.1.1 for details of the imputation of first/last administration date.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

2.5.1.1 Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug and any combination partner, if applicable:

Duration of exposure to study treatment (*days*) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

FGF401 single agent:

Duration of exposure to study treatment is calculated by using the date of first/last administration of study treatment defined in section 2.1.1.3.

FGF401 in combination with PDR001

Duration of exposure to each component (FGF401, PDR001), as well as duration of exposure to study treatment, is calculated by using the date of first/last administration of study treatment and each component defined in section 2.1.1.3.

2.5.1.2 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components, respectively.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations. The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the Dose Administration eCRF.

For patients who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods.

2.5.1.3 Dose intensity and relative dose intensity

Dose intensity (DI) for s with non-zero duration of exposure is defined as follows:

DI (dosing unit/unit of time) = Actual Cumulative dose (dosing unit) / Duration of exposure (unit of time).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (dosing unit/unit of time) = Planned Cumulative dose (dosing unit) / Duration of exposure (unit of time).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (dosint unit/unit of time) / PDI (dosing unit/unit of time).

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components.

2.5.1.4 Dose reductions, interruptions or permanent discontinuations

The number of who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions, and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not consider a dose reduction. Only dose change is collected in the CRF,

number of reductions will be derived programmatically based on the change and the direction of the change.

2.5.2 Prior, concomitant and post therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Any concomitant therapies starting prior to or after the start of study treatment will be listed. Also, antineoplastic therapy since discontinuation of study treatment will be listed.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 2.8.2.1 Adverse events). No imputation will be performed for concomitant medication end dates.

2.5.3 Compliance

Compliance to the study treatment will be summarized in terms of the RDI or percentage of patients who took a predefined percentage of the number of prescribed. The predefined RDI categories are < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of Subjects falling in each category will be presented.

2.6 Analysis of the primary objective

2.6.1 FGF401 single agent

2.6.1.1 Phase I part

Statistical hypothesis, model, and method of analysis

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.

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

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

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

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 $\theta_{fasted} = \left(log(\alpha_{fasted}), log(\beta_{fasted})\right)$ and $\theta_{fed} = \left(log(\alpha_{fed}), log(\beta_{fed})\right)$ 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:

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

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

Prior distributions for μ_{exch} and $\mathbf{\Sigma}_{exch}$ 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 $\mathbf{\Sigma}_{exch}$ 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 $\mathbf{S}_w = \begin{pmatrix} \tau_{w1}^2 & c\tau_{w1}\tau_{w2} \\ c\tau_{w1}\tau_{w2} & \tau_{w2}^2 \end{pmatrix}$ are the mean vector and covariance matrix.

The specification of prior distributions is described in protocol 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 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 protocol Section 6.2.3.

Reports of DLT analysis

Following reports will be produced based on the dose determining set:

- A plot of posterior interval probabilities at the time of database lock will be presented in the body of the CSR;
- Summary of the DLTs with onset during the evaluation period (phase I part only) by primary system organ class, preferred term: recommendations at the time of database lock will be included in the body of the CSR, for each DEM, summary of recommendations will be included in Appendix 16.1.9 of the CSR;
- Listing of inferential results from the BHLRM at the time of database lock, will be included in Appendix 16.1.9.

2.6.1.2 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 of the study protocol, 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 ORR, the proportion of patients having BOR of either confirmed CR or PR, of an individual tumor type will be summarized. These analyses will only be provided for tumor type with which there are at least 10 enrolled patients. Otherwise, data will only be listed.

2.6.2 FGF401 in combination with PDR001

2.6.2.1 Phase I part

Statistical hypothesis, model, and method of analysis

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

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

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:

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

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.

Prior specification

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the FGF401 single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$, the PDR001 single agent parameters $\log(\alpha_2)$, $\log(\beta_2)$ and the interaction parameter η.

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$ and $\log(\beta_1)$ for FGF401, $\log(\alpha_2)$ and $\log(\beta_2)$ for PDR001, and the interaction parameter η. A meta-analytic-predictive (MAP) approach is used to derive a weakly informative prior distribution for the single-agent model parameters based upon available DLT data.

Description of the meta-analytic-predictive (MAP) approach

The aim of the MAP approach is to allow variable heterogeneity of the dose-DLT data from historical study (i.e., CFGF401X2101) and derive a prior distribution for the logistic parameters $\big(\log(\alpha^*),\ \log(\beta^*)\big)$ for the new trial.

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical study s $(s = 1, \ldots, S)$. The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$
$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$
$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi), \qquad \text{s} = 1, \ldots, \text{S}$$
$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

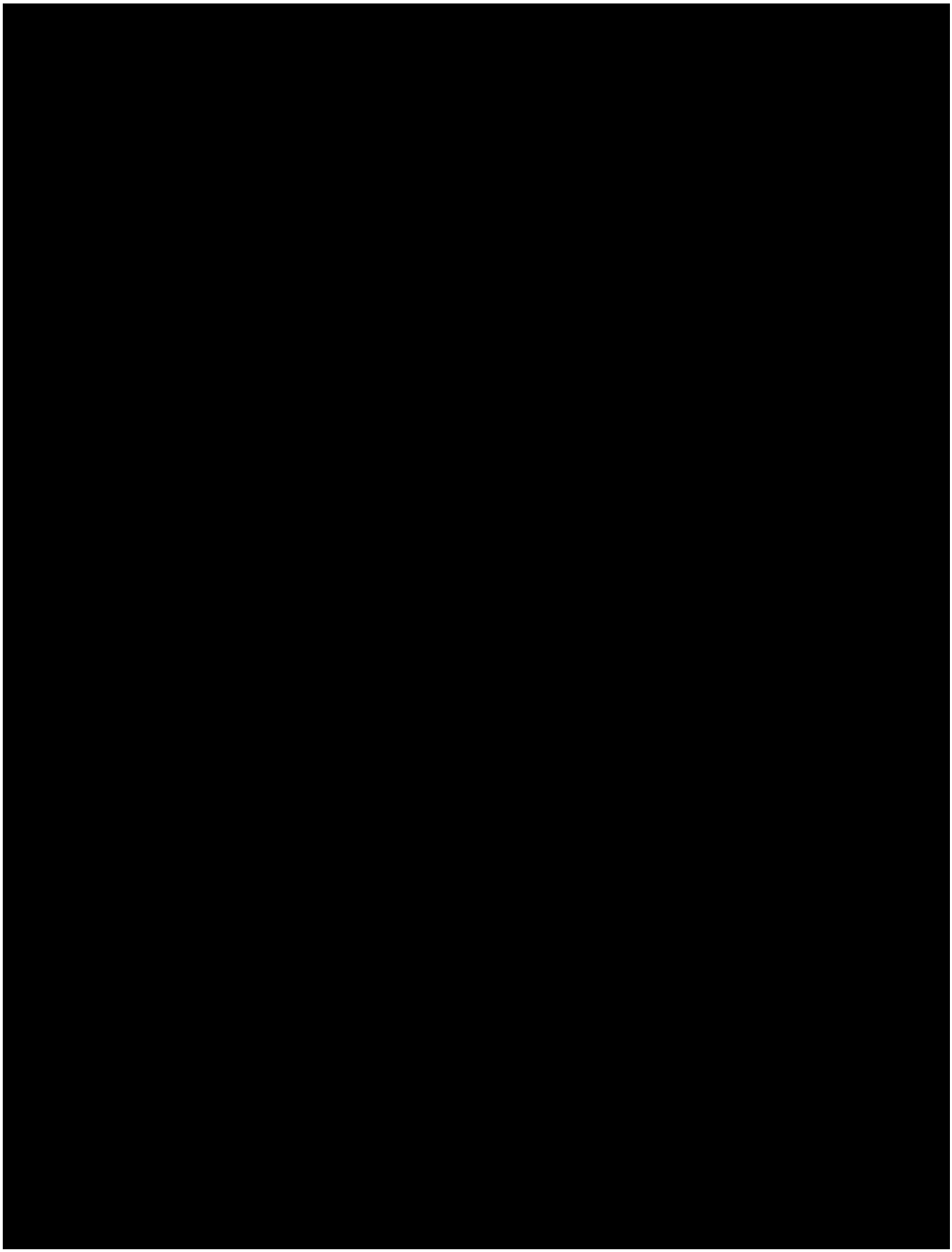
The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation ρ. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

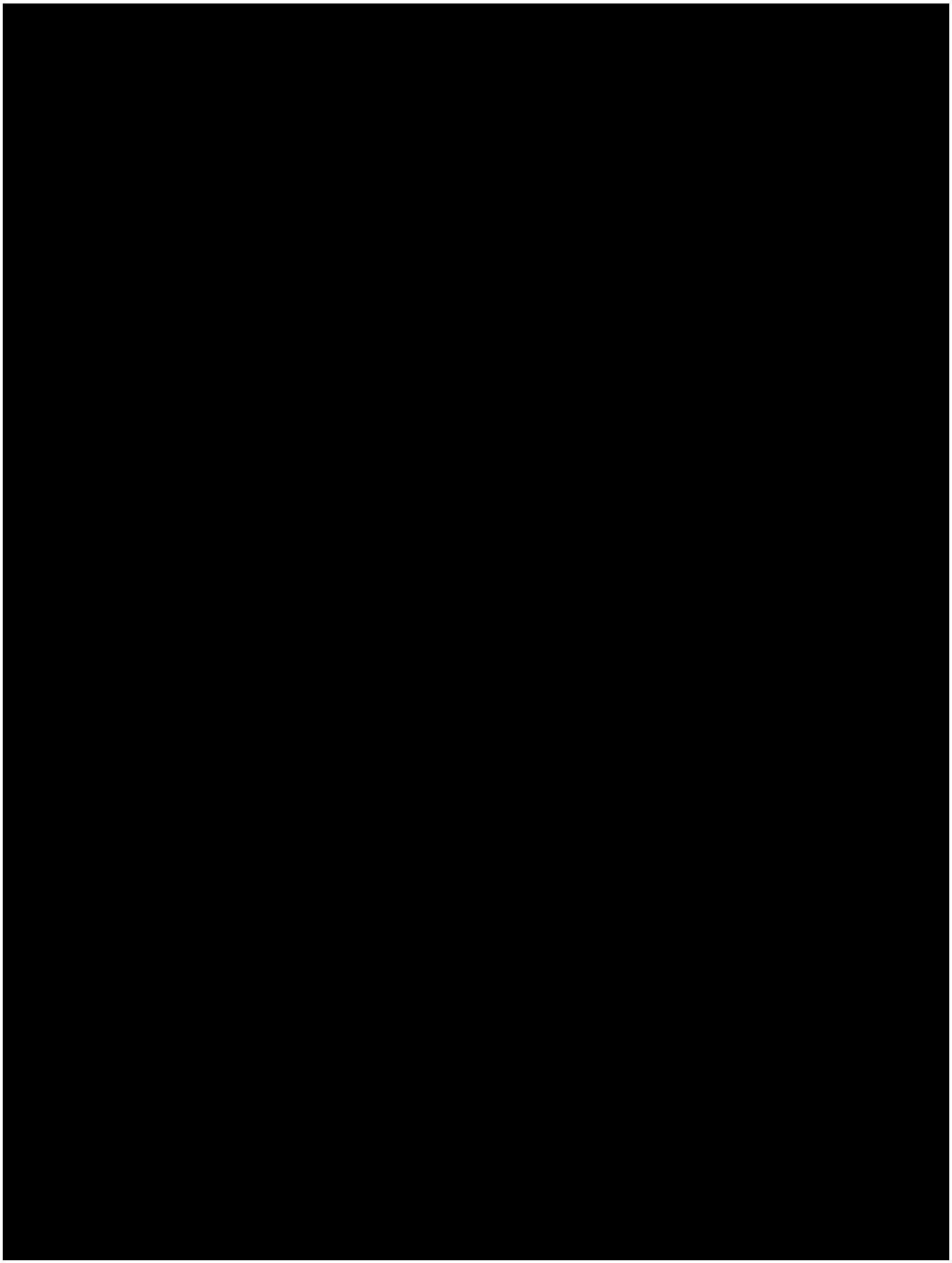
- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for ρ.

The MAP prior for FGF401 and PDR001 single agent parameters in the combination part of the study, $\left(log(\alpha^*), log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, S)$$

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 3.4.0. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike H 1974).





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 protocol Section 6.2.3.

Reports of DLT analysis

Following reports will be produced based on the dose determining set:

- A plot of posterior interval probabilities at the time of database lock will be presented in the body of the CSR;
- Summary of the DLTs with onset during the evaluation period (phase I part only) by primary system organ class, preferred term: recommendations at the time of database lock will be included in the body of the CSR, for each DEM, summary of recommendations will be included in Appendix 16.1.9 of the CSR;
- Listing of inferential results from the BLRM at the time of dabase lock, will be included in Appendix 16.1.9.

2.7 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.8 Analysis of secondary objective(s)

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

2.8.1 Efficacy analysis

Evaluation of anti-tumor activity will be based on investigator assessment of overall lesion response according to RECIST v1.1 (see Protocol Appendix 1) and irRC (only for the FGF401 in combination with PDR001 part; see Protocol Appendix 9). The endpoints used to evaluate anti-tumor activity are BOR, ORR, PFS, TTP, OS, DCR, and DOR using the FAS.

Assessment by irRC (only for the FGF401 in combination with PDR001 part)

For irRC the key difference from RECIST in the assessment of these endpoints is the recommendation that irPD be confirmed at least 4 weeks after the criteria for irPD are first met. A single assessment of irPD followed by a subsequent assessment of irSD or better will be considered as a pseudo-progression, these are not considered as progression events for the purposes of analysis. Where irPD is confirmed by a second assessment, the date of the first of these two assessments is then the date of progression. For Subjects who have ended treatment without a valid confirmation assessment, for the purposes of analysis the single assessment of irPD will be treated as a confirmed irPD. At time of analysis there may be Subjects whose last adequate assessment is an unconfirmed irRC progression but who are continuing treatment. In these cases that progression will be treated as a confirmed progression for the primary analysis, and sensitivity analysis of time to event endpoints may be conducted in which the Subject is censored at the time of last adequate assessment. Additional definitions and derivation rules for irRC are provided in protocol Appendix 9.

Best overall response (BOR)

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence. For assessment per RECIST v1.1, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. For irRC this period is extended to 150 days after last dose in recognition that response to immunotherapy may be delayed.

Overall response rate (ORR)

The ORR is the proportion of patients with a best overall response of CR or PR (RECIST v1.1) or of irCR or irPR (irRC). Confirmed CR and PR will be used for the calculation of ORR.

Disease control rate (DCR)

The DCR is the proportion of patients with a best overall response of CR, PR, or SD (RECIST v1.1) or of irCR, irPR, or irSD (irRC).

Progression free survival (PFS)

For assessment per RECIST v1.1, PFS is the time from date of start of study 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, PFS is censored at the date of last adequate tumor assessment (Protocol Appendix 1 section 14.1.19). For irRC, PFS is defined similarly, but with the date of event defined as the date of the first documented confirmed progression as defined in Section 5.1.4.1, or death due to any cause. For irRC other censoring rules are applied as for RECIST v1.1 (see Protocol Appendix 1 section 14.1.25).

Duration of response (DOR)

The DOR applies only to Subjects with a BOR of confirmed CR or PR (RECIST v1.1) or of confirmed irCR or irPR (irRC). For assessment per RECIST v1.1, DOR is defined as the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to study indication. For assessment per irRC, DOR is defined as the time from the first confirmed response (irCR or irPR), to the date of confirmed progression as defined in Section 5.1.4.1, or death due to study indication.

Overall survival (OS)

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

Time to progression (TTP)

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.

Use of alternative cancer therapy

For both RECIST v1.1 and irRC, if any alternative cancer therapy is taken any subsequent assessments will be excluded from the analysis of endpoints based on tumor response assessments.

2.8.1.1 FGF401 single agent

2.8.1.1.1 Phase I part

BOR, ORR and DCR will be summarized by treatment group. For ORR and DCR accompanying 95% exact binomial CIs will be provided. Waterfall plot will be provided

showing best change in sum of diameters (SOD) for RECIST v1.1. Individual lesion measurements and overall response assessments will be listed by patient.

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. The estimated OS rate at the MTD/RP2D along with 95% CI at 3, 5, 7 and 9 months will be presented. Pooled data of subjects who received the MTD/RP2D under fed and fasted conditions will be used. These analyses will only be provided if there are at least 10 enrolled patients at MTD/RP2D. Otherwise, data will only be listed.

2.8.1.1.2 Phase II part

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, if data permits,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 treatment group.

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.

These analyses will only be provided for tumor type with which there are at least 10 enrolled patients. Otherwise, data will only be listed.

2.8.1.2 FGF401 in combination with PDR001

2.8.1.2.1 Phase I part

BOR, ORR and DCR will be summarized by treatment group. For ORR and DCR accompanying 95% exact binomial CIs will be provided. Waterfall plot will be provided showing best change in sum of diameters (SOD) for RECIST v1.1, and best change in total measurable disease burden (TMTB) for irRC. Individual lesion measurements and overall response assessments will be listed by patient.

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.

2.8.2 Safety analyses

The Safety set will be used for summaries and listings of safety data with the exception of dose limiting toxicities (DLTs) for which the DDS will be used.

2.8.2.1 Adverse events (AEs)

2.8.2.1.1 Data handling

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

2.8.2.1.2 Data analysis

AE Summaries

AE summaries will include all AEs occurring during on-treatment period. Additionally, for the patients receiving PDR001, summaries will be produced using all treatment related AEs starting or worsening during the on-treatment or post-treatment periods. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs starting during the post-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the "all patients" column.

The following summaries for AEs occurring during the on-treatment period will be produced by treatment:

- Overview of adverse events and deaths (number and % of patients who died, with any AE, any SAE, any dose reductions/interruptions, AE leading to discontinuation)
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment);
- Seriousness (SAEs and non-SAEs);
- Leading to treatment discontinuation;
- Leading to dose interruption/adjustment;
- Leading to fatal outcome;

The following listings will be produced:

- All adverse events (safety set)
- Adverse events among patients who were not treated (all screened patients)

In combo part only, the following summaries will be produced for all AEs starting or worsening during the on-treatment or post-treatment periods (within 150 days after the date of last administration of study treatment):

- AEs related to study treatment by SOC and PT;
- SAEs related to study treatment

Considering the limited number of patients enrolled in the combination arm no specific summary tables or listing for AESIs will be provided.

Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment arm, system organ class and preferred term.

All deaths will be listed for the safety set, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g. among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2.2 Laboratory data

2.8.2.2.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria

for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

2.8.2.2.2 Imputation rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium as defined in the previous section.

2.8.2.2.3 Data analysis

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.7).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Shift tables using CTC grades to compare baseline to the worst on-treatment value;
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

2.8.3 Other safety data

2.8.3.1.1 ECG and cardiac imaging data

The average of the ECG parameters at that assessment should be used in the analyses.

12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained central/local for each patient during the study. ECG data will be read and interpreted centrally locally

The number and percentage of patients with notable ECG values will be presented by treatment arm.

- QT, or QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
- Increase from baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New value of > 120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.3.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse (beats per minute), systolic and diastolic blood pressure (mmHg).

Values measured during the post-treatment period will be flagged in the listings. The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment arm.

Table 2-8 Criteria for notable vital sign values

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase >= 10% from baseline	decrease >= 10% from baseline

Systolic blood pressure (mmHg)	>=180 and increase from baseline of >=20	<=90 and decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 and increase from baseline of >=15	<=50 and decrease from baseline of >=15
Pulse rate (bpm)	>=100 and increase from baseline of >25%	<=50 and decrease from baseline of >25%
Body temperature (°C)	>= 39.1	--

2.8.4 Pharmacokinetic analysis

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

PK parameters will be determined for all PK-evaluable patients with noncompartmental method(s) using Phoenix WinNonlin version 6.4 or above (Pharsight, Mountain View, CA). For FGF401, the PK parameters include but may be not limited to those listed in Table 10-7. For PDR001, PK parameters would be limited to Cmax, Tmax, AUClast andT1/2.

All the concentration data are presented in summary table of the concentration data, where the minimal concentration (Cmin) is included. Therefore, Cmin was not additionally produced as a stand-alone parameter.

Table 2-9 Non-compartmental 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), in the current situation it equals to AUC0-24h (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma 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 (volume x time-1)
Racc	Accumulation ratio calculated using AUCtau at steady state divided by AUCtau at Day 1

2.8.4.1 Data handling principles

Only PK blood samples with date and time and for which the last prior dose dates and times are adequately and correctly 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, based on the judgement of PK analyst.

All concentrations below the lower limit of quantitation (LLOQ) 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, unless otherwise stated under the Pharmacokinetic Analysis Set.

2.8.4.2 Data analysis set

All pharmacokinetic data analyses and PK summary statistics will be based on PAS.

2.8.4.3 Basic tables, figures, and listing

Concentration data

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

Descriptive statistics will be presented for all pharmacokinetic parameters. Only for the parameter Tmax, the descriptive statistics including median, min and max will be summarized. Otherwise noted, mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum will be summarized for other PK parameters. In addition, 90% CI will be provided for Racc.

Zero concentrations will not be included in the geometric mean calculations. Missing concentrations or PK parameter values will not be imputed. A listing of derived PK parameters per Subject will be produced by treatment group.

2.8.4.4 Dose proportionality

Analysis of dose-proportionality will be performed if at least three doses of FGF401 are investigated.

Cmax and AUCtau will be used for dose proportionality analysis using the power model. The power model empirical relationship between a PK parameter and dose is of the form

$$\mathrm{PK} = \mathrm{Exp}(\alpha)\ (dose)^{\beta},$$

where "PK" represents the PK parameter AUCtau or Cmax. For analysis, this equation is log-transformed (natural log), obtaining the equation

$$\log_e(PK) = \alpha + \beta\ \log_e(dose),$$

The slope beta measures the dose-proportionality between dose and the PK parameter.

The 90% confidence interval of the slope for each parameter will be computed from the model and presented in the summary table. The dose proportionality assessment it exploratory analysis due to insufficient power to demonstrata dose proportionality.

Food effect PK analysis

As exploratory analysis, exposure measures (Cmax, Tmax and AUC) of FGF401 will be compared among patients taking study drug under different feeding regimens (fasted or fed-light meal) as appropriate.

2.8.4.5 Immunogenicity

2.8.4.5.1 Sample ADA status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier).

- Samples testing negative in the screening assay are defaulted to be negative in the confirmatory assay (i.e., no confirmatory testing is done).
- Samples testing positive in the screening assay are then subjected to a confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier).
- Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the titration assay.

The following properties of each sample will be provided in the source data:

- Positivity in confirmatory assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of the ADA response

Sample ADA status will only be listed. It is determined based on the following definitions:

- *ADA-inconclusive sample*:
    - Sample where ADA confirmatory assay is negative and PDR001 PK concentration at the time of IG sample collection is >= *55* µg/mL or missing.
- *Unevaluable sample*: Sample where ADA confirmatory assay is not available.
- *Determinant sample:* Sample that is neither ADA-inconclusive nor unevaluable.
- *ADA-negative sample*:
    - Determinant sample where ADA confirmatory assay is negative and PDR001 PK concentration at the time of IG sample collection is < *55* µg/mL.
- *ADA-positive sample*: Determinant sample where ADA confirmatory assay is positive.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample:

    - *treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline.

- *treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least twofold greater than the ADA-positive baseline titer.
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than twofold greater than the ADA-positive baseline titer.

2.8.4.5.2 Patient ADA status

Any IG sample collected after 150 days of the last dose of PDR001 and FGF401 will not be used for summaries or derivations and will only be included in the listing.

The following overall summaries will be provided using the Safety Analysis Set:

- Treatment-boosted ADA-positive: number and percent of subjects with at least one treatment-boosted ADA-positive sample. The denominator is the number of subjects with an ADA-positive sample at baseline.
- Treatment-induced ADA-positive: number and percent of subjects with at least one treatment-induced ADA-positive sample. The denominator is the number of subjects with an ADA-negative sample at baseline.
- ADA-negative: number and percent of subjects with no treatment-induced or treatment-boosted ADA-positive sample.
- ADA incidence (i.e. % ADA-positive): number and percent of subjects with at least one treatment-induced or treatment-boosted ADA-positive sample.

The following summaries, both overall and by timepoint (including baseline), will be provided using the FAS. For summaries by timepoint, the denominator is the number of subjects at that timepoint with determinant samples:

- ADA prevalence: number and percent of subjects with at least one ADA-positive sample.

A listing will be provided by subject with supporting information (i.e. ADA sample status at each timepoint (including titer for positive samples) and subject ADA status).

[redacted]

2.10 Interim analysis

2.10.1 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 the Protocol 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 (Protocol Section 8.5 and Section 8.6).

2.10.2 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 the Protocol Section 6.2.3.

3 Sample size calculation

3.1.1 FGF401 single agent

3.1.1.1 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 Protocol 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 the Protocol 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.

3.1.1.2 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 3-1 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 Protocol Section 4.1. Considering a drop-out rate of 15%, the PoS is 90.6%.

Table 3-1 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 3-2 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 Protocol Section 4.1. Considering a drop-out rate of 15%, the PoS is 87.7 %.

Table 3-2 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 3-3 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 one or more responders with 20 patients are 0.642, 0.878 and 0.997, respectively.

Table 3-3 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

3.1.2 FGF401 in combination with PDR001

3.1.2.1 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 the Protocol 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.

4 Change to protocol specified analyses – CSR Section 9.8.3

Because the enrollment of this study has been halted for business reason since 03Jul18 and the phase II part of the FGF401+PDR001 combination will not start, all analysis plan related to the phase II part of the FGF401+PDR001 combination arm are removed.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

5.1.1.1 Data handling

5.1.1.1.1 Data Imputation for the last administration

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

Patients with missing start dates are to be considered missing for all study treatment component related calculations described in Section 2.5.1.2 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.1.1.2 Data Imputation of the first administration

Patients with missing start dates are generally considered missing for all study treatment component related calculations described in Section 2.5.1.1 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

However, if the dosing information at C1D1 is entered on the PK DAR page, the date on this page will be used to impute the first administration date. Before imputing the date, it will be checked that the date is not after the second administration or after the end date of the first record.

5.1.2 AE date imputation

A missing AE start date will be imputed using the logic matrix described in Table 5-1.

Table 5-1 Imputation rules for a partially missing AE start date

	AEM missing	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEY missing	Not imputation	Not imputation	Not imputation	Not imputation
AEY<TRTY	(D)	(C)	(C)	(C)
AEY=TRTY	(B)	(C)	(B)	(A)
AEY>TRTY	(E)	(A)	(A)	(A)

AEM=Month AE started, AEY=Year AE started
TRTM=Month treatment started, TRTY=Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

AE start date relationship	Imputation
(A) After treatment start or uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before treatment start	15MMMYYYY
(D) Before treatment start	01JULYYYY
(E) After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for missing/incomplete AE end dates.

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). No imputation will be performed for concomitant medication end dates.

5.1.3.1 Prior therapies date imputation

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that scenario (B) will be replaced to be 'start date of study treatment - 1'. (see Section 5.1.2)

End Date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.3.2 Post therapies date imputation

Start date:

Imputed date = max (End of Treatment date + 1, first day of the month), if day is missing;

Imputed date = max (End of Treatment date + 1, 01JAN), if day and month are missing.

Imputed date = End of treatment date +1, if the date is completely missing.

End date:

No imputation.

5.1.3.3 Other imputations

Diagnosis and extent of cancer

When a date is recorded as a partial date, the missing day is imputed to the 15th of the month (e.g. DEC2007 imputed to 15DEC2007), and if the day and month are both missing then to 1st of July of that year (e.g. 2007 imputed to 01JUL2007).

5.2 Definition and derivation rules for irRC

5.2.1 Total measurable disease burden

In irRC target and new measurable lesions are used to evaluate total measurable tumor burden (TMTB). TMTB is the sum of diameters (SOD) of all target and new measurable lesions. Similar to RECIST v1.1 where SOD of the target lesions is used for determination of target lesion response, for irRC TMTB is used for determination of target and new measurable lesion response.

5.2.1.1 Best percentage change from baseline in TMTB

Best percentage change from baseline in TMTB is defined as the percentage change from baseline to the smallest measured post-baseline TMTB occurring at or before the time of confirmed irPD.

5.2.2 Assessment of disease progression

To facilitate analysis, each assessment of progression is categorized as one of three types: pseudo progression, confirmed progression and unconfirmed progression.

5.2.2.1 Pseudo-progression

Subjects with a single irPD, followed by an assessment of irSD or better will be considered to have a pseudo-progression (pPD). For the purposes of analysis, pseudo-progressions are not treated as progression events.

5.2.2.2 Confirmed progression

Confirmed progression 1 (type 1, cPD1) is declared if a Subject has 2 consecutive tumor assessments at least 4 weeks (28 days) apart both showing disease progression. Assessments with an UNK response or PD assessments < 28 days after initial PD, are discarded.

The first PD is flagged as cPD1 while all subsequent PDs are flagged as xPD1.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irPD 2 irUNK 3 irPD (Assessment 1 + 30 days)	• Assessment 3 is ≥28 days after Assessment 1 • Assessment 3 represents confirmation of irPD at assessment 1 • Assessment 1 irPD is flagged cPD1 • Assessment 3 irPD is flagged xPD1
1 irSD 2 irPD 3 irPD (Assessment 2 + 20 days) 4 irPD (Assessment 2 + 30 days)	• Assessment 3 is < 28 days after Assessment 2 • Assessment 4 is ≥ 28 days after Assessment 2 • Assessment 4 represents confirmation of irPD at assessment 2 • Assessment 2 irPD is flagged cPD1 • Assessment 3 and 4 irPDs are flagged xPD1

Confirmed progression 2 (type 2, cPD2) is declared if a Subject discontinues treatment following a single PD with no subsequent assessments ≥ 28 days later. Assessments with an UNK response or PD assessments < 4 weeks (28 days) after initial PD, are discarded. Discontinuation of treatment is obtained from EOT case report form.

The assessment is flagged as cPD2 and subsequent PDs (<28 days after first PD) are flagged as xPD2.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irSD 2 irPD - EOT	• Subject withdraws after initial progression (Assessment 2) without confirmation • Assessment 2 irPD is flagged as cPD2
1 irPD 2 irPD (Assessment 1 + 20 days) - EOT	• Assessment 2 irPD is <28 days after Assessment 1, so does not represent confirmation • However, Subject has completed treatment • Assessment 1 irPD is flagged cPD2 • Assessment 2 irPD is flagged xPD2

5.2.2.3 Unconfirmed progression

Patients with a single irPD, and no assessment of irSD or better (assessment with an irUNK response or irPD assessments < 4 weeks after initial irPD, are discarded) continuing treatment at the time of the analysis will be considered as unconfirmed (uPD).

5.2.3 Best overall response

Assessment of BOR will be based on all assessments up to and including the first assessment of irPD (cPD1, cPD2, or uPD). Assessments made more than 150 days after EOT will be excluded. Assessments made after start of new anti-cancer therapy will be excluded.

BOR will be defined with the following hierarchy:

irCR	Two consecutive determinations of irCR ≥28 days (4 weeks) apart Non-consecutive assessments of irCR may also result in BOR of irCR if all intervening assessments are irUNK
irPR	Two determinations of irPR (or better) ≥28 days (4 weeks) apart The two determinations of irPR (or better) may be separated by one or more assessments of irSD, but may not be separated by an assessment of irPD
irSD	At least one irSD assessment (or better) >[42 days (6 weeks)] after the start of study treatment
irPD	Event flagged as cPD1, cPD2 or uPD ≤[84 days (12 weeks)] after the start of study treatment
irUNK	All other cases

5.2.4 Time to event analyses:

5.2.4.1 Progression events

PDs flagged as pPD are not included in time to event analyses.

Patients are classified as follows:

0	No event (censored)
1	Confirmed PD (cPD1 or cPD2)
2	Unconfirmed PD (uPD)

For the primary analysis of time to event endpoints, both confirmed and unconfirmed progression will be included as progression events with date of progression being the date of

the assessment flagged as cPD1, cPD2 or uPD according to the algorithm defined in Section 5.2.2.

A sensitivity analysis of time to event endpoints may be conducted in which Subjects with unconfirmed PD are treated as censored, with date of last adequate assessment = visit date for assessment flagged uPD.

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

Assessment date

Assessment date is defined as for RECIST v1.1 (Protocol Appendix 1 section 14.1.25).

Start date

Start date is as defined for RECIST v1.1 (Protocol Appendix 1 section 14.1.25).

End dates for time to event variables

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

- Date of death (recorded on the end of treatment disposition page, the end of post treatment phase disposition page, or the survival information page).
- Date of death as recorded on death CRF
- Date of progression is as defined in Section 5.2.4.1.
- 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 progression 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 start of study treatment is used.

Note: for sensitivity analyses of time to event endpoints ongoing Subjects with an unconfirmed progression may be censored at time of last assessment.

5.2.4.3 Censoring reason

Censoring reason is derived as for RECIST v1.1(Protocol Appendix 1 section 14.1.39).

5.2.4.4 Duration of response

Duration of response is defined as a time interval between the first date of confirmed PR/CR and the date of progression as defined in Section 5.2.4.1. Intervening assessments of pPD are excluded from the assessment.

Date of confirmed response

Response (irPR or irCR) should be confirmed by a second assessment no less than 4 weeks after the first assessment showing response. Date of response is then the date of the first of these two assessments. For confirmation of irCR the two assessments must be consecutive (intervening assessments of irUNK are permissable). For confirmation of irPR the two assessments do not need to be consecutive, but must not be separated by a pseudo-progression event.

The table below shows a hypothetical data scenarios with programming instructions.

Sequence of assessments	Instructions
1 irPR 2 irPD 3 irPR 4 irPR	• The first PR (assessment 1) is followed by a pseudo-progression (assessment 2) and is therefore not confirmed • Subsequently the Subject has a irPR (assessment 3) which is confirmed at the following assessment (assessment 4) • The BOR for this Subject is irPR, with date of confirmed irPR equal to the date of assessment 3

5.3 Details of pharmacokinetic data analysis

For the assessment of dose proportionality, the following SAS code will be used:

```
PROC MIXED DATA=dataset METHOD=reml;
  MODEL log_PK_parameter = log_dose / ddfm=kr solution
                        alpha=0.1 cl;
RUN;
```

6 References

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