Official Title: A Phase II Basket Study of the Oral Selective Pan-FGFR Inhibitor Debio 1347 in Subjects With Solid Tumors Harboring a Fusion of FGFR1, FGFR2 or FGFR3

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Statistical Analysis Plan

A Phase II basket study of the oral selective pan-FGFR inhibitor Debio 1347 in subjects with solid tumors harboring a fusion of FGFR1, FGFR2 or FGFR3

Investigational Medicinal Product: Debio 1347

Debiopharm Study Number: Debio 1347-201

SPONSOR:

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Version Final 2.0 dated on **09 April 2021**

Relevant Study Information

Study number:	**Debio 1347-201**
Study title:	A Phase II basket study of the oral selective pan-FGFR inhibitor Debio 1347 in subjects with solid tumors harboring a fusion of FGFR1, FGFR2 or FGFR3.
Study phase:	II
Protocol version and date:	Version 3 dated 2020-07-16
Sponsor	Debiopharm International S.A., Ch. Messidor 5-7, P.O. Box 5911, CH-1002 Lausanne, Switzerland
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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration versus time curve
BLOQ	Below limit of quantification
BOR	Best overall response
[redacted]	[redacted]
CI	Confidence interval
C_{max}	Maximum serum concentration
CR	Complete response
[redacted]	[redacted]
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
FGFR	Fibroblast growth factor receptor
FWER	Family-Wise error rate
H0	Null hypothesis
H1	Alternative hypothesis
HR	Heart rate
IMP	Investigational medicinal product
IRC	Independent review committee
ITT	Intent-to-treat
K-M	Kaplan-Meier
LOQ	Limit of quantification
MedDRA	Medical dictionary for regulatory activities
mITT	Modified ITT
NCI	National cancer institute
NE	Not evaluable
ORR	Objective response rate

Abbreviation	Definition
OS	Overall survival
PA2	Protocol amendment 2
PD	Progressive disease
PFS	Progression-free survival
[redacted]	[redacted]
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
P-R	Interval between the P and R waves
[redacted]	[redacted]
PS	Performance status
PT	Preferred term
Q1	25th percentile
Q3	75th percentile
QD	Once daily
[redacted]	[redacted]
QRS	Distance between the Q and S waves
QT	Interval between the Q and T waves
QTcF	QT interval corrected for heart rate using Fridericia 's formula
QTcSS	Study specific QT correction
RECIST	Response evaluation criteria in solid tumors
RR	Interval between 2 consecutive Rwaves
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SDlog	Standard deviation of the log-transformed values
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNM	Tumor-Node-Metastasis
[redacted]	[redacted]
WHO-DD	World health organization drug dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analyses planned to be performed for the study Debio 1347-201 entitled "A Phase II basket study of the oral selective pan-FGFR inhibitor Debio 1347 in subjects with solid tumors harboring a fusion of FGFR1, FGFR2 or FGFR3". The SAP is compliant with the study protocol version 3, dated of July 16th 2020.The SAP will be finalized prior to the database lock for the main analysis.

The rationale for Protocol Amendment 2 (PA2) was

- The results of data monitoring reviews of pooled data (Section **Error! Reference source not found.**) showed that the antitumor activity of Debio 1347 was lower than initially assumed at the time the protocol was developed. Considering that further enrolment is unlikely to substantially change the magnitude of the efficacy observed up to now, Debiopharm decided to permanently halt the enrolment in the study after consultation with the IDMC on June 10th, 2020.

After implementation of PA2:

- After consenting to PA2, on-treatment subjects will no longer be assessed for efficacy in the study, but only for safety.
- Off-treatment subjects will not be followed for disease status or survival in the study, but only for safety up to 30 days post last dose of Debio 1347.
- Subjects will complete study participation at 30 days after the last dose of Debio 1347. In the case of off-treatment subjects with >30 days and <2 years follow-up at the time of PA2 implementation, then these subjects can complete study participation immediately.

The SAP will pre-specify the statistical consideration for the analysis of study data to ensure validity of study findings and conclusions regarding study objectives.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the efficacy of Debio 1347 in terms of objective response rate (ORR) in subjects with solid tumors harboring fibroblast growth factor receptor (FGFR) 1-3 gene fusion/rearrangement.

2.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the efficacy of Debio 1347 in terms of duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS).
2. To assess the safety of Debio 1347.
3. To assess exposure-response relationships versus efficacy and safety (notably QTcF).

[redacted]

3 STUDY ENDPOINTS

In subjects enrolled late in the study, PA2 shortens the data collection period for efficacy data. After PA2 is in force, efficacy assessments and central radiological review will no longer be performed in on-treatment subjects, and off-treatment followed up for disease status and survival will no longer be performed in off-treatment subjects.

After PA2 is in force, onl for on-treatment and off-treatment subjects will be collected using standard institutional practice and local laboratory testing in accordance with the protocol study plan to support the ongoing safety assessments.

3.1 Primary Endpoint

The primary endpoint is ORR, defined as the proportion of subjects with a best overall response (BOR) of partial or complete response as centrally measured by RECIST 1.1 criteria.)

3.2 Secondary Endpoints

The secondary endpoints are:

1. DOR, defined as the time from the date of the initial partial response (PR) or complete response (CR) to date of the first documented progressive disease (PD) or death due to any cause.
2. DCR, defined as the proportion of subjects with a BOR of CR, PR or SD .
3. PFS, defined as the time from the start date of treatment to date of the first documented PD or death due to any cause.
4. OS, defined as the time from the start date of treatment to date of death due to any cause.
5. Proportion of subjects with treatment-emergent adverse events (TEAEs) assessed by the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 and proportion of subjects with serious adverse events (SAEs).
6. Debio 1347 plasma exposure (C_{trough}, area under the curve [AUCτ] and any other PK parameters as deemed appropriate) and relationships with efficacy and safety endpoints; Debio 1347 plasma concentration (C)-QTcF relationship based on electrocardiogram (ECG) and PK matching time-points. These relationships will be derived only if deemed appropriate, depending on the safety and efficacy outcomes and data availability.

[redacted]

[redacted]

4 STUDY DESIGN AND TREATMENT

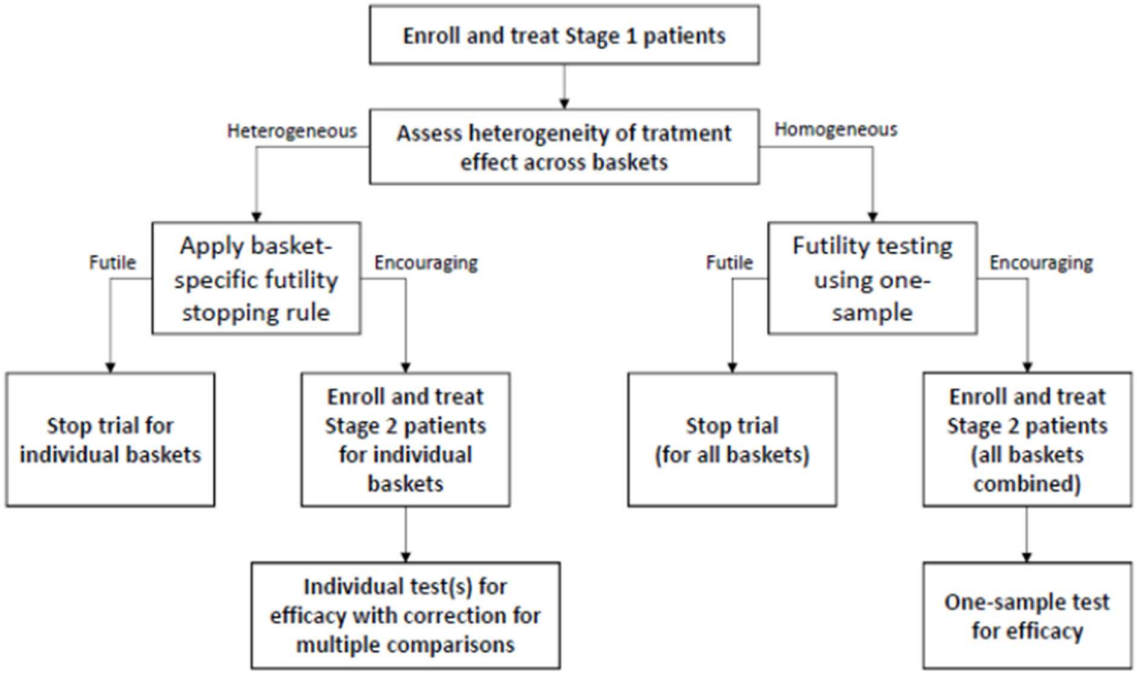
4.1 Study Design

4.1.1 Study design before protocol amendment 2

This is a multicenter, basket, two stage, adaptive single arm Phase II study to examine the efficacy of Debio 1347 administered at the recommended Phase II daily dose of 80 mg in subjects with solid tumors harboring FGFR1-3 gene fusion/rearrangement. The study will include 3 cohorts of subjects comprising biliary tract cancer (Cohort 1), urothelial cancer (Cohort 2) and, in Cohort 3, all other solid tumor histologies not included in cohort 1 or cohort 2, such as non-small cell lung cancer (NSCLC), head and neck cancer, thyroid cancer, oral cancer, breast cancer, prostate cancer and others but excluding primary brain tumors.

Stage 1 will require 27 evaluable subjects across the three cohorts assuming an equal accrual rate per cohort. Stage 2 will require 86 evaluable subjects across all cohorts or per individual cohort depending on results of assessments scheduled at the end of Stage 1 (see Figure 1).

Figure 1 - Graphical algorithm representing study design (extracted from Cunanan et al. (2017))



Subjects will be treated with Debio 1347 once daily (QD) in 28-day cycles until the occurrence of disease progression (clinical or radiologic) or unacceptable toxicity. Subject safety (AEs) and survival will be followed-up respectively for 30 days after the last Debio 1347 dose and every 12 weeks from treatment end until death or loss to follow-up but no longer than for a total of 2 years after the last subject has discontinued treatment. Disease status will be followed-up every 12 weeks only in subjects without PD from treatment end until PD, death or loss to follow-up but no longer than for a total of 2 years after the last subject has discontinued treatment.

An Independent Data Monitoring Committee (IDMC) will be established to review safety, tolerability and efficacy data, as well as to monitor the overall conduct of the study at regular intervals. Interim analysis will also be discussed by IDMC.

The IDMC meeting schedule, purpose, roles and responsibilities will be outlined in a separate document, the IDMC Charter.

4.1.2 Study design after protocol amendment 2

The interim analysis was not conducted as planned (as detailed in section 10.8.2). Based on an initial statistical review of pooled data, the antitumor activity for Debio 1347 is lower than initially assumed at the time the protocol was developed. Debiopharm decided to permanently halt the enrollment in stage 1 of the study after consultation with the IDMC on June 10th, 2020.

The subsequent protocol amendment 2 (PA2) was implemented to modify the study design in the following ways:

- All ongoing patients (on-treatment subjects and off-treatment subjects still under follow-up) will be re-consented to PA2.
- Subjects showing clinical benefit may remain on-treatment with Debio 1347 until a condition to stop treatment is met.

- After consenting to PA2, on-treatment subjects will no longer be assessed for efficacy in the study, but only for AE, SAE and AESI as described in the pared down study plan of PA2 (**Error! Reference source not found.**).
- Off-treatment subjects will not be followed for disease status or survival in the study, but only for AE, SAE and AESI up to 30 days after the last dose of Debio 1347.
- Subjects will complete study participation at 30 days after the last dose of Debio 1347. In the case of off-treatment subjects with >30 days and <2 years follow-up at the time of PA2 implementation, then these subjects can end (i.e. complete) study participation immediately.
- Subsequent efficacy data collected through standard institutional care practice in on-treatment and off-treatment subjects will not be collected in the eCRF.
- No further IDMC meetings will be required.

4.2 Study Treatments

Subjects will receive Debio 1347 tablets at the dose of 80 mg QD from Day 1 to Day 28 in 28-day cycles until occurrence of any of the criteria described in the protocol requiring treatment discontinuation.

5 RANDOMISATION AND BLINDING

Not applicable.

6 SAMPLE SIZE

A basket two stage adaptive design will be used to assess the efficacy of Debio 1347 in terms of ORR, (Cunanan et al. 2017).

With 27 evaluable subjects in Stage 1 and 86 evaluable subjects in Stage 2, the study will have approximately 90% power to reject the null hypothesis that ORR ≤ 15% when the true ORR is 30% in at least one of the baskets, using a one-sided exact binomial test at an overall significance level of 5%. The sample size for Stage 2 is for a pooled sample across baskets in case homogeneity is shown at end of Stage 1, or for one active basket taken into Stage 2 in case of heterogeneity. Sample size and design operating characteristics were determined using simulations, see Table 1.

Assuming homogeneity across baskets and a 10% drop out, the study would enroll approximately 125 subjects.

If homogeneity is declared at the interim analysis, 86 participants across three cohorts will be enrolled in stage 2. Otherwise, 86 participants will be enrolled in stage 2 in each of the cohorts continuing into stage 2.

Table 1 - Power and expected sample size based on 1000 simulations using Cunanan et al. (2017) algorithm

Assumed ORR of 15% for inactive cohorts and 30% for active cohorts	**Number of truly active cohorts**			
	0 Active	**1 Active**	**2 Active**	**3 Active**
Marginal Power				
FWER	5%	16%	39%	NA
Power 1 active cohort	3%	64%	88%	92%
Power 2 active cohorts	3%	15%	87%	93%

Nt period Power 3 active cohorts	4%	15%	39%	93%
Expected sample size	111	148	165	161
% Homogeneity rejected at end of stage 1	38%	54%	57%	46%
Cohort 1 continuing to stage 2	25%	52%	54%	42%
Cohort 2 continuing to stage 2	26%	36%	53%	42%
Cohort 3 continuing to stage 2	24%	35%	35%	42%
Homogeneity accepted at end of stage 1	62%	46%	43%	54%
Continuing to stage 2	47%	41%	42%	54%

7 ANALYSIS POPULATIONS

7.1 Screened Population

The Screened population consists of all subjects who have signed the informed consent.

7.2 Intent-to-Treat Population (ITT)

The intent-to-treat (ITT) population consists of all subjects who received study drug.

Receiving study drug is considered to have taken at least 1 full dose (80 mg Debio 1347) of study drug. Subjects will be analyzed according to their assigned cohort.

7.3 Modified Intent-to-Treat Population (mITT)

The modified intent-to-treat (mITT) population consists of all subjects in the ITT population whose gene fusion/rearrangement has been confirmed by central testing.

A patient has gene fusion/rearrangement confirmed by central testing if the patient appears in the Caris central lab external dataset and has a result of gene fusion/rearrangement being present. Subjects will be analyzed according to their assigned cohort.

7.4 Per Protocol Population (PP)

The per protocol (PP) population consists of all subjects in the ITT population who have undergone radiographic assessment at baseline (i.e., tumor assessment screening visit), received at least one dose of study drug, had both baseline and post-baseline disease and had no critical protocol deviation that may have an impact on efficacy endpoints.

Having radiographic assessment at baseline and baseline disease is considered met if inclusion criterion 7 (having measurable disease according to RECIST 1.1 at baseline) is Yes.

Having post-baseline disease is clarified as requiring at least 1 post-baseline disease assessment.

Critical protocol deviations that may have an impact on efficacy endpoints are defined as (also see Section 13.6):

- Violation of any inclusion/exclusion criteria at entry.
- Actual cumulative dose below 75% of planned cumulative dose from date of first dose to date of end of cycle 4 or date of treatment discontinuation, whichever occurs first.
- Subject data indicate a major protocol deviation other than the criteria defined above, that potentially affects efficacy assessment and is identified prior to database lock.

7.5 Safety Population (SAF)

The Safety population consists of all subjects who received study drug.

Receiving study drug is considered to have taken at least 1 full dose or partial dose of study drug.

7.6 PK Population (PKP)

The PK population (PKP) will include subjects who received one or more doses of Debio 1347 and have at least one PK concentration result available.

Receiving one or more doses of Debio 1347 is considered to have taken at least 1 full dose of study drug.

7.7 C-QT Population (CQP)

The C-QT population (CQP) will include subjects in PK population who has at least one matching ECG evaluation and PK sampling.

The C-QT population will be used for exposure-response (C-QTcF) analysis. However, whether the exposure-response analysis is performed will depend on the outcome of safety and efficacy analyses and data availability.

A matching ECG evaluation and PK sampling pair is defined as follows: measurements for which the elapsed time between the two is within a time window of +/- 30 minutes (for pre-dose and 7h post-dosing time points) and +/- 20 minutes (for 1h and 3h post-dosing time points). Pairs for which the elapsed time between the two assessments is outside these windows will be excluded from the analysis. If more than 30% of pairs are excluded at 1h and 3h time points because of deviations from the protocol-defined window for ECG measurement (within 20 min of PK samplings), the analysis will be repeated using a time window of +/-30 min for 1h and 3h post-dose time points.

8 DATA HANDLING

8.1 Missing Data

In subject listings, incomplete dates will be presented as collected in the electronic case report form (eCRF). In order to identify whether an AE is treatment-emergent or whether a medication is prior or concomitant, partial dates missing the day, or both the day and month of the year will be considered as outlined below.

8.1.1 Adverse Event

When the day of onset of an AE is missing:

- If month and year of onset of an AE is the same as the month and year of date of first administration of the study drug:
    - If AE end date contains a full date and end date is earlier than study treatment start date, then the missing onset day is entered as the 1st of the month.
    - Otherwise, the missing onset day is entered as the day of date of first administration of the study drug.
- If month and year of onset of an AE is not the same as the month and year of date of first administration of the study drug, the missing onset day is entered as 1st of the month.

When the day and month of onset of an AE are missing:

- If year of onset of an AE is the same as the year of date of first administration of the study drug:

- If AE end date contains a full date and end date is earlier than study treatment start date, then the missing onset day and month are imputed as January 1st.
- Otherwise, the missing onset day and month are imputed as the day and month of date of first administration of the study drug

- If year of onset of an AE is not the same as the year of date of first administration of the study drug, the missing onset day and month are imputed as January 1st.

If AE onset date is completely missing:

- If AE end date is on or after the date of first administration of the study drug, then onset date is set to date of first administration of the study drug.
- If AE end date is prior to the date of first administration of the study drug, then onset date is not imputed, and AE is not considered as treatment-emergent.

If AE end date is prior to the date of first administration of the study drug, then onset date is not imputed, and AE is not considered as treatment-emergent.

If AE end day is missing, then end day will be imputed as last day of the month, or end date of the on-treatment period, whichever is earlier

If AE end day or month are missing, then end day will be imputed as last day of the month and end month will be imputed as December, or end date of the on-treatment period, whichever is earlier.

If AE end date is completely missing, then imputed as end date of the on-treatment period.

8.1.2 Concomitant Medications

End date: Missing day will be imputed as the last day of the month, and missing month will be imputed as December.

Start date: Missing day will be imputed as the first day of the month, and missing month will be imputed by January. If the start date is completely missing, then:

- If the end date is prior to the date of first administration of the study drug, then the medication is considered as prior
- If the end date is prior to or on the date of last administration of the study drug, then the medication is considered as prior and concomitant
- If the end date is completely missing or after the date of last administration of the study drug, then the medication is considered as prior, concomitant and post.

8.2 Coding

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) v23.0 (March 2020). Prior and concomitant medications will be coded using the last available World Health Organization Drug Dictionary (WHO-DD) Global B3 March 2020.

8.3 Handling of Values Below (or Above) a Threshold

For statistical and graphical summaries of the safety laboratory tests, values below or above the limit of detection (e.g. '< 3' or '>500') are substituted with the lower/upper limit of detection (e.g. '< 3' is substituted by '3', '> 500' is substituted by '500'). In data listings, the values will be shown as collected, e.g. including the < or > sign.

In the PK analysis, Debio 1347 plasma concentrations below the limit of quantification (BLOQ) will be set to ½ LOQ for calculation of all summary statistics.

Handling of BLOQ values for deriving PK parameters will be described in the dedicated Data Analysis Plan for population PK analysis (cf. study Debio 1347-507).

8.4 Handling of Unscheduled Assessments or Retests

In case of pre-dose retests, the latest value will be used in the analysis. The post-dose retests and the unscheduled assessments will not be used in the summary statistics but will be used in the derivation of endpoints that are not related to a specific timepoint (i.e. worst-case assessment, BOR, time to event endpoints, etc.). They will also be displayed in listings.

9 GENERAL STATISTICAL CONSIDERATIONS

9.1 General Conventions

The statistical analysis described below corresponds to analysis planned for the study. Any deviation from the planned analysis will be documented in clinical study report.

Continuous data will be presented in the form of descriptive statistics, as the number of observations, mean, standard deviation, minimum, 25th percentile (Q1), median, 75th percentile (Q3) and maximum.

Categorical data, including ordinal data, will be presented using contingency tables with absolute and relative frequencies. Missing will be considered as a category and included in the calculation of percentages, unless otherwise stated.

For time-to-event endpoints, Kaplan Meier (K-M) estimates will be provided and include number and percentage of events/censored, 25th (Q1), median and 75th (Q3) survival time and associated 95% confidence interval (CI, if applicable), survival rate and 95% CI at pre-specified time points. For the CIs, these will be Brookmeyer-Crowley for the survival time quartiles and Greenwood for the survival rate.

For PK parameters and concentrations, summary statistics in the tabulation will include number of non-missing value, number below the LOQ, mean, standard deviation, Q1, Q3, 90% CI of the arithmetic mean, coefficient of variation (CV%), median, minimum, maximum, geometric mean, 90% CI of the geometric mean, geometric standard deviation [calculated as: geo standard deviation = exp (SDlog)] and geometric CV% [calculated as: geo CV% =SQRT(exp(SDlog2)-1)*100%; where SDlog is the standard deviation of the log-transformed values].

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, confidence intervals, Q1 and Q3 will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. Percentages will be reported with one decimal place. The CV% is reported as a percentage with 1 decimal place.

Baseline measurement is the latest value collected prior to the administration of study drug.

All data analyses will be performed using SAS® statistical software version 9.4 or higher, R software version 3.3 or higher and NONMEM®.

9.2 Dates, Times and Days

Study day is defined as:

- (Date of event) – (Date of first dose of study drug) + 1, if the event is on or after the date of first dose;
- (Date of event) – (Date of first dose of study drug), if the event is before the date of first dose.

9.3 Timing of Analyses

The timing of the first IDMC meeting was as planned:

- The first IDMC meeting will take place after 15 subjects have either been on treatment for at least 8 weeks or discontinued the study treatment.

The timing of the second IDMC meeting was planned to be conducted at same time as the interim analysis:

- The second IDMC meeting will be convened to review the Interim Analysis results. An interim analysis will be conducted at end of Stage 1 to assess ORR homogeneity across baskets as well as futility. A minimum of 4 subjects per cohort and a maximum of 13 subjects per cohort will be required for the end of Stage 1 analysis (see Section 10.8 for full details of the planned interim analysis).
- However, the second IDMC meeting took place with 63 evaluable subjects (30, 4, and 29 in cohorts 1, 2 and 3, respectively).

The timing of the main analysis will be modified by Protocol Amendment 2 as follows:

- The main analysis will be conducted with all the safety and efficacy data after the last subject has consented to Protocol Amendment Nº 2. The data from this analysis will be used to write an abbreviated clinical study report (CSR).

The final descriptive analysis will be conducted as planned:

- A final descriptive analysis focused on safety will be conducted after the last subject has completed the EOS visit.
- As the study ended earlier than expected, it is decided to conduct the main analysis and the final descriptive analysis at the same time after the last subject has completed the EOS visit.

9.4 Treatment Period

The treatment period (or on-treatment period) is defined as from date of first administration of study treatment until 30 days after the last dose of study treatment or date of death, whichever is earlier.

10 STATISTICAL ANALYSIS METHODS

All tables and figures will be presented by cohort and overall. Since the interim analysis did not perform a homogeneity assessment of the primary endpoint, then the by-cohort and total groups will be presented for the efficacy endpoints.

10.1 Disposition of Subjects, Demographic and Baseline Data

10.1.1 Subject Disposition

Number (%) of patients will be presented by total patients only for All Screened Subjects, in the following:

- Screened (patients with informed consent) (number only)
- Screened but not enrolled and by reason for not enrolling

Number of patients will be presented for:

- Enrolled but not treated
- Treated

Number (%, calculated using denominator of treated patients) will be presented for

- End of treatment status (ongoing at data cut-off, discontinued) and by reason for treatment discontinuation
- End of study status (ongoing at data cut-off, discontinued) with reason for study discontinuation
- Subject in ITT, mITT, Safety, PP, PK population.

Number (%) of patients will be summarized in each analysis population (ITT, mITT, PP, SAF and PKP). Reasons for exclusion from PP will be provided:

- No measurable disease at baseline (inclusion criterion 7)
- No post-baseline disease assessment
- Violation of eligibility criteria at entry
- Treatment compliance <75%
- Other major protocol deviation that potentially affects efficacy assessment

Subjects per country and sites will be tabulated for the ITT, mITT and PP.

All subject disposition data will be presented in data-listings. Screening failure and reasons will be listed separately. Reason of exclusion from each analysis population will be listed.

10.1.2 Protocol Deviations

All deviations from the protocol will be reviewed and classified as minor, major or critical prior to the database lock for the main analysis. The full list of possible protocol deviations will be included in the study protocol deviation log which will include the classification.

Major (combined categories of major and critical) protocol deviations will be summarized by type of deviation, cohort and total in the ITT population. A by-subject listing of all protocol deviations will be presented and will include the type of deviation and description.

10.1.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the ITT, mITT and PP.

Demographic and baseline characteristics include:

- Age (years) at the time of consent, defined as (Informed consent date – date of birth+1) / 365.25. In case, the date of birth is not allowed to be collected due to local constraints, age entered in the eCRF will be used. Missing day of date of birth will be imputed as the 15th and missing month will be imputed as June.
- Gender, race, ethnicity and child-bearing potential (for females only).
- Height (cm), weight (kg), body mass index (kg/m^2) = weight / height^2.
- Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline.

A by-subject listing showing the demographic characteristics will be provided.

10.1.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) medical dictionary version 22.0 or later. Number (%) of subjects with medical history classified by system organ class (SOC) and preferred term (PT) will be summarized for the ITT, mITT and PP.

Medical history will be provided in a data-listing including the information on: SOC, PT, reported term, start and end date.

10.1.5 Disease Characteristics

Baseline disease characteristics will be summarized on ITT population. The analysis will be repeated on mITT and PP population.

Baseline disease characteristics include:

- Primary location of tumor.
- Histopathologic Grade
- Stage at initial diagnosis
- Initial Tumor-Node-Metastasis (TNM) stage.
- Time since initial diagnosis (years), defined as (treatment start date – initial diagnosis date)/365.25.
    - Missing day of initial diagnosis will be imputed at the 15th and missing month will be imputed as June. If the entire date is missing, date of initial diagnosis will be imputed as the earliest start date of prior anti-cancer therapy
- Site of local/metastatic disease
- Time since diagnosis of locally advance/metastatic disease (years), defined as (treatment start date – date of diagnosis of locally advance/metastatic disease) / 365.25.
    - Missing day of initial diagnosis will be imputed at the 15th and missing month will be imputed as June.
- FGFR fusion/alteration at screening (whether central lab or local lab) .

10.1.6 Prior anti-cancer treatments

Prior anti-cancer treatments will be summarized for the ITT, mITT and PP.

Number (%) of patients with prior anti-cancer treatments will be summarized for:

- Any prior treatment with radiotherapy.
- Any prior systemic therapy.
- Any prior surgery.
- Number of previous lines of anti-cancer systemic therapy as continuous and categorical (1, 2, 3, >3).

Prior anti-cancer treatments will be summarized by ATC level 2, 4 and WHO preferred name. Best response to last prior cancer systemic therapy will also be reported.

Additionally, prior anti-cancer treatments will be listed and will include:

- Prior radiotherapy: location, dose, start and end date, number of fraction days.
- Prior anti-cancer therapy: therapy agent, therapy class, intent of therapy, line number, start and end date, reason for therapy, best overall response reached.
- Prior surgery.

10.2 Efficacy Analyses

The efficacy analysis will be performed on the ITT population as the primary analysis. All efficacy analyses will be repeated on the mITT and PP population as supportive analysis, unless otherwise stated.

PA2 shortens the data collection period for efficacy data. Compared to early enrolled subjects, the later enrolled subjects will systematically have less tumor response assessments at PA2 implementation and time to event variables censored at date of last dose. There will be no additional statistical considerations to specifically address these systematic differences between earlier and later enrolled patients, and therefore, the planned statistical methods remain same as before PA2 was implemented.

Also, since the homogeneity assessment at interim analysis was not conducted, the efficacy endpoints will be analyzed and reported by cohort and pooled total subjects.

10.2.1 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of subjects with a best overall response of confirmed PR or confirmed CR based on RECIST 1.1 criteria.

Best overall response (BOR) is defined as the best response designation for each subject that is recorded between the date of first administration of the study drug and the date of first documented disease progression per RECIST 1.1, the date of non-permitted concomitant treatment, date of a new systemic therapy or the date of study withdrawal for other reason, whichever occurs first.

Stable Disease (SD) will be considered as BOR only if the assessment is performed at least 6 weeks (i.e. 42 days) after the date of first dose of the study drug. If the minimum time from first dose of the study drug is not met when SD is observed, then subject's BOR depends on the subsequent assessments. A subject lost to follow-up after the first SD assessment will be considered not evaluable (NE). Subjects without any radiologic tumor assessment will be considered as NE. Patients who die with no evaluable RECIST assessments will be assigned to the NE category.

Per RECIST 1.1 criteria, CR and PR needs to be confirmed at a subsequent assessment, at least 4 weeks (i.e. 28 days) after initial overall response assessment of CR/PR. Confirmed BOR will be derived as described in RECIST 1.1 guidance summarized in Table 2.

Table 2 - Confirmation of BOR based on RECIST 1.1

Overall response first time point	Overall response subsequent time point*	Confirmed BOR
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE
PR	CR	PR

Overall response first time point	Overall response subsequent time point*	Confirmed BOR
PR	PR	PR
PR	SD	SD
PR	PD	SD, if minimum criteria for SD duration met. Otherwise PD
PR	NE	SD, if minimum criteria for SD duration met. Otherwise NE
NE	NE	NE

*After the first post-baseline assessment of CR/PR, a subject may have fluctuations in target lesion assessment, but as long as they have a subsequent assessment showing response at least 4 weeks after the initial assessment without an assessment of progressive disease, this would qualify as an objective response. For instance, if a subject has PR-SD-PR or PR-NE-PR at consecutive tumour assessments, the objective response would qualify for PR.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Subjects with a clinical progression determined by investigator will be scheduled to have a radiologic tumor assessment as per protocol. The response designation determined per RECIST 1.1 criteria using this scan will be included in the derivation of BOR. In case the planned scan is not performed, then the clinical progression will be used in the BOR derivation.

10.2.1.1 Primary Analysis

The primary analysis will be performed at the time of the main analysis for ORR as centrally measured by an Independent Review Committee (IRC) based on RECIST 1.1 criteria.

IRC tumor response variables will be measured by 2 independent assessors. A patient will have the same 2 assessors through out the trial. There are in total 4 assessor, named in numerical sequence: 'Independent Assessor 1', 'Independent Assessor 2', 'Independent Assessor 5', 'Independent Assessor 6'. The Banook Imaging Review Charter ensures categorical tumor response variables will agree between the independent assessors. The continuous tumor size variables can differ between independent assessors. An overall independent assessor analysis value will be derived for use in the primary analysis. The overall independent assessor analysis value for tumor size will be the value from the first alphabetically sorted assessor (e.g. if 'Independent Assessor 2' and 'Independent Assessor 5', the overall tumor size will be assigned as from 'Independent Assessor 2').

The hypothesis tested will be according to the decision taken at the interim analysis:

- Scenario 1: If the ORR homogeneity assumption is met at the end of Stage 1 and futility is not met, then the hypothesis will be:

  H0: ORR ≤ 15% against H1: ORR > 15 %

  The statistical comparison will be conducted on the combined Stage 1 and Stage 2 pooled sample of data across cohorts using a one sided binomial exact test at an alpha level of 5%.

- Scenario 2: If the ORR homogeneity assumption is not met at the end of Stage 1, then a decision will be made at the time of interim analysis to further continue the study with only 1 cohort or multiple cohorts. Then the hypothesis tested at the final stage will be:

  H0: ORR ≤ 15% against H1: ORR > 15 % in each continuing cohort

The statistical comparison will be conducted within each continuing cohort on the combined Stage 1 and Stage 2 pooled sample using a one sided binomial exact test at an alpha level of 5% divided by the number of non-futile cohorts.

As such, the overall family wise error rate (FWER) for the study is controlled under 5%.

However, the interim analysis to examine homogeneity of ORR across cohorts was not conducted after data monitoring review observed a lower than expected antitumor activity in the pooled group. Therefore, the main analysis will present the analysis of ORR (and other efficacy endpoints) by cohort and pooled total subjects.

Objective response rate will be summarized using frequencies and percentages. The Clopper-Pearson CI will be calculated using a one-sided binomial exact test at an alpha level as described in the hypothesis testing will be presented for all stage combined.

The best overall response (CR, PR, SD, PD and NE) will be summarized descriptively to show the number and percentage of subjects in each response category. The PD category will be further split into radiological progression (RECIST) and clinical progression. (Note: In case a patient has both radiological and clinical progression, the patient will be summarized under radiological progression.) The NE category will be further split into SD observed before 6 weeks , incomplete post baseline assessment and death without post-baseline assessment.

10.2.1.2 Supportive Analysis

The analysis on ORR will be repeated on mITT and PP population as supportive analysis.

A sensitivity analysis will also be performed on the ORR based on local investigator assessment of response using RECIST 1.1 criteria. This analysis will be performed using the ITT population and repeated using the mITT and PP populations.

10.2.2 Duration of Response

Duration of response (months) is defined as (date of the first documented disease progression or death due to any cause, whichever occurs first - date of the initial response (PR or CR) + 1)/30.4375. It will be calculated only for subjects with a confirmed BOR of CR or PR.

The following censoring rules will be applied:

- Subjects who do not experience death or PD, nor initiate a new anti-cancer therapy will be right-censored at the date of their last adequate tumor assessment (i.e. a tumor assessment not showing NE).
- Subjects having initiated a new anti-cancer therapy before experiencing death or PD will be right-censored at the date of their last adequate tumor assessment prior to initiation of a new anti-cancer therapy.
- Subjects who experienced death or PD after two or more consecutive missing or inadequate tumor assessments will be right-censored at their latest adequate assessment before death or PD.

Median, 25^{th} and 75^{th} percentile of duration of response with corresponding 95% CI (using log-log transform, Brookmeyer and Crowley 1982) will be provided. Duration of response rate with corresponding 95% CIs (using Greenwood's formula and log-log transform, Kalbfleisch and Prentice 2002) at every 6 months will be presented. A K-M plot for DOR will be presented.

Swimmer plots will be used to graphically present the DOR for each subject with a documented response of CR or PR.

The analysis on DOR will be based on the IRC evaluation on using the ITT population as the main analysis. Supportive analyses will be performed using:

- IRC evaluation of response on mITT and PP populations.
- Investigator assessed response on ITT, mITT and PP populations.

10.2.3 Disease Control Rate

Disease control rate is defined as number of subjects with a BOR of confirmed CR, confirmed PR or SD at least 6 weeks after the date of first dose of the study drug.

Disease control rate will be summarized using frequencies and percentages. In addition, 95% Clopper-Pearson CI will be provided.

The analysis of DCR will be performed based on the independent review committee (IRC) evaluation on the ITT population as the main analysis. Supportive analyses will be performed using:

- IRC evaluation of response on mITT and PP populations.
- Investigator assessed responses on ITT, mITT and PP populations.

10.2.4 Tumor Size

The change in tumor size will be calculated for each subject in the ITT population as the percentage change from baseline in the sum of longest diameters of target tumor lesions at each assessment time point. The percentage change from baseline in the sum of longest diameters will be summarized for each scheduled assessment. In addition, the largest decrease in tumor size or the minimum increase from baseline in the absence of a reduction from baseline based on all post baseline assessments will be summarized descriptively. Waterfall plots will be used to present graphically the largest decrease for each subject by BOR. Reference lines will be drawn at +20% and -30% change from baseline. A waterfall plot will be presented for each cohort and overall.

10.2.5 Progression-Free Survival

Progression-free survival (months) is defined as (date of the first documented disease progression or death due to any cause, whichever occurs first - start date of treatment + 1)/30.4375.

The following censoring rule will be applied:

- Subjects who do not experience death or PD, nor initiate anti-cancer therapy will be right-censored at the date of their last adequate tumor assessment (i.e. a tumor assessment not showing NE).
- Subjects having initiated a new anti-cancer therapy before experiencing death or PD will be right-censored at the date of their last adequate tumor assessment prior to initiation of a new systemic therapy.
- Subjects who experienced death or PD after two or more consecutive missing or inadequate tumor assessments will be right-censored at their latest adequate assessment before death or PD.
- Subjects without a baseline or post-baseline assessment will be right-censored at the date of first administration of the study drug.

Progression-free survival rate at every 6 months will be presented with the corresponding 95% CIs will be estimated using the K-M method. A K-M plot for PFS will be presented.

The analysis will be performed on PFS calculated based on IRC assessment of response on the ITT population as the main analysis. Supportive analyses will be performed using:

- IRC evaluation of response on mITT and PP populations.
- Investigator assessed response on ITT, mITT and PP populations.

10.2.6 Overall Survival

Overall survival (months) is defined as (date of death due to any cause - the start date of treatment +1)/30.4375. Subjects with no documented death will be censored at the last date known to be alive (i.e. latest date collected in the eCRF).

Survival rate at every 6 months will be presented with the corresponding 95% CIs will be estimated using the K-M method. A K-M plot for OS will be presented.

10.2.7 Subgroup Analysis

ORR and DOR analysis will be repeated, whenever appropriate, on the following subgroups:

- By gender (Male, Female)
- By Region: North America, Europe, Rest of the world
- Subjects with a dose-reduction (as per investigator's decision)
- Subjects with no dose-reduction (as per investigator's decision)

However, given the early stopping and reduced data collection after PA2, it is deemed not appropriate to perform the subgroup analysis.

10.3 Safety Analyses

The safety analysis will be conducted in the Safety Population.

After PA2 is in force, safety assessments for on-treatment and off-treatment subjects will be performed using standard institutional practice and using local laboratory testing. Generally, safety data collected by the local investigator at all clinic visits but only AEs, SAE and AESI will be recorded in the eCRF to support the ongoing safety assessments up to 30 days after last administration of study treatment. The changes in study design relating to safety data include:

- Central clinical laboratory will no longer be performed but will use the local laboratory. Central and local laboratory data will be analyzed together, i.e. not separate analysis for each data source. Shifts in central and local laboratory values will be determined based on the central or local reference range, respectively.
- ECGs will not necessarily be collected in triplicate and central reading will not be performed. Local reading of ECGs will be used. Central and local ECG readings will be analyzed together.

10.3.1 Extent of Exposure

Extent of exposure and compliance derived from the subject diary eCRF and "Date of last study drug intake" in the End Of Treatment CRF form will be summarized as continuous for the following:

- Date of last dose of study drug, defined as the "Date of last study drug intake" in the End Of Treatment CRF form, or if missing will be replaced with the date of last non-zero drug intake in the subject diary.
- Treatment duration (weeks), defined as (date of last dose of study drug – date of first dose + 1)/7.
- Number of completed 28-day cycles, defined as the integer value of floor(treatment duration in days/28). (Note: Report only the median, quartiles, min and max.)
- Cumulative dose (mg), defined as (total number of tablets taken during the study)*20 mg. Note: In the case of incomplete diary data over the treatment duration of the subject, the days

with missing tablet counts will be assumed to have a zero tablet count in the calculation of cumulative dose over the treatment duration.

- Planned cumulative dose (mg), defined as (treatment duration in days)*80 mg. For any period where there is a dose reduction this will be multiplied by 60 mg. Note: This quantity is not summarized, but only used in calculation of treatment compliance.
- Dose intensity (mg/day), defined as

  Cumulative dose (mg) / Treatment duration (days)
- Treatment compliance (a k.a. relative dose intensity) (%), defined as

  *(Cumulative dose (mg) / Planned cumulative dose (mg))*100*
- Treatment compliance for first 4 cycles (%), defined as

  (Cumulative dose (mg) for the period where dose date – treatment start date ≤ 112 /

  planned cumulative dose for first 4 cycles (112 multiplied by 80 mg. For any period where there is a dose reduction this will be multiplied by 60 mg.)

Number (%) of patients will be presented for:

- Treatment compliance (>=75, <75%)
- Treatment compliance for first 4 cycles (>=75, <75%)
- Number of dose reductions: 0 or 1 dose reduction. (Note: Patients will be permanently discontinued if a second reduction is necessary and thus having >1 dose reduction should not occur according to protocol procedures. If the >1 dose reduction category occurs it will additionally be displayed).

A study day between study drug first dose day and last dose day (or last dose at data cut off) is considered a temporary interruption if the number of tablets taken is 0 or missing as recorded in the subject diary eCRF. An episode of temporary interruption is defined as a run of consecutive days with temporary interruption that are flanked before and after by a day with >0 number of tablets taken. Patients can have multiple episodes of temporary interruption. Temporary interruptions based on the subject diary eCRF will be summarized as follows:

- Number (%) of patients with at least one interruption.
- Number of episodes of interruption per patient presented as continuous and as categories (0, 1, 2, >2).
- Maximum duration of an interruption episode (days) presented as continuous and as categories (0, >=1 to <5, >=5 to <7, >=7 to <14, >=14 days). This is a summary of the episode with the maximum number of consecutive days with interruption.
- Cumulative duration of interruption days presented as continuous and as categories (0, >=1 to <5, >=5 to <7, >=7 to <14, >=14 days). This is the total interruption days summed over all episodes.

Temporary interruptions due to AE will be defined using the AE CRF data:

- Number (%) of patients with at least one interruption due to AE, defined as having at least 1 TEAE with “Action taken with Study Drug” = Temporarily Interrupted.
- Number of interruptions due to AE per patient presented as continuous and as categories (0, 1, 2, >2), defined as counting unique start dates of TEAEs with “Action taken with Study Drug” = Temporarily Interrupted. (Note: Counting only unique start dates ensures we do not double-count AEs that are part of the same interruption episode.)

Subject diary information will be presented in a data listing.

10.3.2 Adverse Events

Treatment-emergent AE (TEAE) is defined as any AE that either starts or worsens in severity on or after the first administration of the study drug and within 30 days of the last administration of the study drug. Details for handling of completely/partially missing dates are described in Section 8.1.1.

Related TEAE will be defined as any TEAE with "reasonable causal relationship" relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship. When assessing investigator reported relationship to study drug of the AEs, if an AE reported multiple times changes in causal relationship during an analysis period for a subject, the event is considered related.

When summarizing severity of the AEs, if there are multiple AEs of the same preferred term but different grade, the AE with the maximum CTCAE grade will be reported. If the AE term (SOC and PT) is reported more than once, one of them with missing grade, and at least another with non-missing grade, the maximum CTCAE grade will be chosen from the non-missing grade values and the missing grade can be ignored. If all are of missing grade, then summary of the AE term will include a "missing" category of CTCAE grade.

An overview of adverse events table will be presented for the following AEs overall and includes the number and percentage of subjects and the number of events:

- All TEAE
- TEAE related to study drug
- TEAE with grade 3 or higher
- TEAE with grade 3 or higher related to study drug
- TEAE by worst severity grade according to the NCI-CTCAE v5.0 criteria
- Serious TEAE
- Serious TEAE related to study drug
- TEAE leading to fatal outcome
- TEAE leading to dose reduction
- TEAE leading to temporary treatment interruption
- TEAE leading to permanent treatment discontinuation
- TEAE leading to any dose modification (discontinuation, dose reduction, interruption)
- Treatment emergent adverse event of special interest (AESI – as defined in protocol)
- AESI with grade 3 or higher
- AESI related to the study drug
- AESI with grade 3 or higher related to study drug

The number and percentage of subjects with the following AEs will be summarized using descriptive statistics by SOC and PT. SOCs and PTs within each SOC will be displayed in decreasing order of frequency. Subjects who have multiple events in the same PT within a SOC or the same SOC will be counted only once by worst grade (if applicable).

The following by-subject listings will be provided.

- Adverse events
- Serious adverse event

- Adverse events leading to treatment discontinuation
- Adverse events leading to fatal outcome
- AESI
- All deaths and reasons.

These listings will include at least: SOC, PT and reported term, treatment-emergent flag, AE start date/time, AE end date/time, action taken with study medication, relationship, seriousness, CTCAE grade and outcome.

10.3.3 Clinical Laboratory Evaluations

Laboratory parameters include:

- Hematology: Complete blood count with differential, hemoglobin and platelet count.
- Chemistry: Total protein, albumin, indirect and total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, calcium, and magnesium), serum phosphate, serum creatinine, creatinine clearance, uric acid, bile salts.
- Urinalysis: Red blood cells/hpf, white blood cells/hpf, casts/hpf, protein dipstick test.

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. Both local and central laboratory values will be included in the analysis.

Hematology and chemistry parameters and corresponding changes from baseline will be presented as descriptive statistics by visit.

Shift tables based on the NCI-CTCAE v5.0 toxicity grading (and ad hoc grading criteria for hyperphosphatemia) will be presented for each hematology and chemistry parameter between baseline and the highest post-baseline NCI-CTCAE v5.0 toxicity grade or the highest post-baseline ad hoc grading criteria for hyperphosphatemia (including unscheduled assessment). The highest toxicity grade can either be above or below the laboratory standard normal range.

For hematology and chemistry parameters without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed post-baseline. Subjects who experienced both low and high laboratory test results will be reported in a separate “Low and High” column. “Low” and “High” column will represent the subjects having only low/high values respectively.

Boxplots of actual values and change from baseline will be presented by visit for selected hematology and chemistry parameters as relevant. Log transformation will be applied if necessary.

Urinalysis parameters will be summarized by visit using descriptive statistics. For categorical urinalysis parameters, missing data will not be considered as a category and the calculation of frequencies will use the number of non-missing observations. Results from the urinary pregnancy test will be listed.

Summary statistics will be presented for subjects with at least one post-baseline phosphate (phosphorus) level above 5.5:

- Time from start of treatment to Phosphate level of 5.5mg/dL or higher, defined as [earliest date where phosphate ≥ 5.5mg/dL] – [date of first administration of the study drug] +1

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hematology	Hemoglobin	Hemoglobin increased	H	g/L	CHG <= 0	0 < CHG <= 20	20 < CHG <= 40	40 < CHG	
Hematology	Hemoglobin	Anemia	L	g/L	LLN <= aval	100 <= aval < LLN	80 <= aval < 100	aval < 80	
Hematology	Leukocytes	Leukocytosis	H	GI/L	aval <= 100			100 < aval	
Hematology	Leukocytes	White blood cell decreased	L	GI/L	LLN <= aval	3 <= aval < LLN	2 <= aval < 3	1 <= aval < 2	aval < 1
Hematology	Lymphocytes	Lymphocyte count increased	H	GI/L	aval <= 4		4 < aval <= 20	20 < aval	
Hematology	Lymphocytes	Lymphocyte count decreased	L	GI/L	LLN <= aval	0.8 <= aval < LLN	0.5 <= aval < 0.8	0.2 <= aval < 0.5	aval < 0.2
Hematology	Neutrophils	Neutrophil count decreased	L	GI/L	LLN <= aval	1.5 <= aval < LLN	1 <= aval < 1.5	0.5 <= aval < 1	aval < 0.5
Hematology	Platelets	Platelet count decreased	L	GI/L	LLN <= aval	75 <= aval < LLN	50 <= aval < 75	25 <= aval < 50	aval < 25
Hematology	Basophils		NA						
Hematology	Basophils/Leukocytes		NA						
Hematology	Eosinophils		NA						
Hematology	Eosinophils/Leukocytes		NA						

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hematology	Ery. Mean Corpuscular Hemoglobin		NA						
Hematology	Ery. Mean Corpuscular HGB Concentration		NA						
Hematology	Ery. Mean Corpuscular Volume		NA						
Hematology	Erythrocyte Cell Morphology		NA						
Hematology	Erythrocytes		NA						
Hematology	Hematocrit		NA						
Hematology	Lymphocytes Atypical		NA						
Hematology	Lymphocytes/Leukocytes		NA						
Hematology	Monocytes		NA						
Hematology	Monocytes/Leukocytes		NA						
Hematology	Neutrophils Band Form		NA						

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hematology	Neutrophils Band Form/Leukocytes		NA						
Hematology	Neutrophils/Leukocytes		NA						
Hematology	Reticulocytes		NA						
Hematology	Reticulocytes/Leukocytes		NA						
Chemistry	Alanine Aminotransferase	Alanine aminotransferase increased	H	U/L	(upcase(bnrind) in ('NORMAL','LOW') and aval <= ULN) or (upcase(bnrind) ='HIGH' and aval <= 1.5*base)	(upcase(bnrind) in ('NORMAL','LOW') and ULN < aval <= 3*ULN) or (upcase(bnrind) ='HIGH' and 1.5*base<aval<=3*base)	(upcase(bnrind) in ('NORMAL','LOW') and 3*ULN < aval <= 5*ULN) or (upcase(bnrind) ='HIGH' and 3*base<aval<= 5*base)	(upcase(bnrind) in ('NORMAL','LOW') and 5*ULN < aval <= 20*ULN) or (upcase(bnrind) ='HIGH' and 5*base<aval<=20*base)	(upcase(bnrind) in ('NORMAL','LOW') and 20*ULN < aval) or (upcase(bnrind) ='HIGH' and 20*base<aval)
Chemistry	Albumin	Hypoalbuminemia	L	g/L	LLN <= aval	30 <= aval < LLN	20 <= aval < 30	aval < 20	

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Chemistry	Alkaline Phosphatase	Alkaline phosphatase increased	H	U/L	(upcase(bnrind) in ('NORMAL','LOW') and aval <= ULN) or (upcase(bnrind) ='HIGH' and aval <= 2*base)	(upcase(bnrind) in ('NORMAL','LOW') and ULN < aval <= 2.5*ULN) or (upcase(bnrind) ='HIGH' and 2*base<aval<=2.5*base)	(upcase(bnrind) in ('NORMAL','LOW') and 2.5*ULN < aval <= 5*ULN) or (upcase(bnrind) ='HIGH' and 2.5*base<aval<= 5*base)	(upcase(bnrind) in ('NORMAL','LOW') and 5*ULN < aval <= 20*ULN) or (upcase(bnrind) ='HIGH' and 5*base<aval<=20*base)	(upcase(bnrind) in ('NORMAL','LOW') and 20*ULN < aval) or (upcase(bnrind) ='HIGH' and 20*base<aval)
Chemistry	Aspartate Aminotransferase	Aspartate aminotransferase increased	H	U/L	(upcase(bnrind) in ('NORMAL','LOW') and aval <= ULN) or (upcase(bnrind) ='HIGH' and aval <= 1.5*base)	(upcase(bnrind) in ('NORMAL','LOW') and ULN < aval <= 3*ULN) or (upcase(bnrind) ='HIGH' and 1.5*base<aval<=3*base)	(upcase(bnrind) in ('NORMAL','LOW') and 3*ULN < aval <= 5*ULN) or (upcase(bnrind) ='HIGH' and 3*base<aval<= 5*base)	(upcase(bnrind) in ('NORMAL','LOW') and 5*ULN < aval <= 20*ULN) or (upcase(bnrind) ='HIGH' and 5*base<aval<=20*base)	(upcase(bnrind) in ('NORMAL','LOW') and 20*ULN < aval) or (upcase(bnrind) ='HIGH' and 20*base<aval)
Chemistry	Calcium Corrected	Hypercalcemia	H	mmol/L	aval <= ULN	ULN < aval <= 2.9	2.9 < aval <= 3.1	3.1 < aval <= 3.4	3.4 < aval
Chemistry	Calcium Corrected	Hypocalcemia	L	mmol/L	LLN <= aval	2 <= aval < LLN	1.75 <= aval < 2	1.5 <= aval < 1.75	aval < 1.5

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Chemistry	Calcium, Ionized	Hypercalcemia	H	mmol/L	aval <= ULN	ULN < aval <= 1.5	1.5 < aval <= 1.6	1.6 < aval <= 1.8	1.8 < aval
Chemistry	Calcium, Ionized	Hypocalcemia	L	mmol/L	LLN <= aval	1 <= aval < LLN	0.9 <= aval < 1	0.8 <= aval < 0.9	aval < 0.8
Chemistry	Creatinine	Creatinine increased	H	umol/L	aval <= ULN	ULN < aval <= 1.5*ULN	(1.5*ULN < aval <= 3*ULN) or (. < 1.5*BASE < aval <= 3*BASE)	(3*ULN < aval <= 6*ULN) or (. < 3*BASE < aval)	6*ULN < aval
Chemistry	Creatinine Clearance	Chronic kidney disease	L	mL/sec	LLN <= aval	1 <= aval < LLN	0.5 <= aval < 1	0.25 <= aval < 0.5	aval < 0.25
Chemistry	Glomerular Filtration Rate	Chronic kidney disease	L	mL/min/ 1.73m2	LLN <= aval	60 <= aval < LLN	30 <= aval < 60	15 <= aval < 30	aval < 15
Chemistry	Magnesium	Hypermagnesemia	H	mmol/L	aval <= ULN	ULN < aval <= 1.23		1.23 < aval <= 3.3	3.3 < aval
Chemistry	Magnesium	Hypomagnesemia	L	mmol/L	LLN <= aval	0.5 <= aval < LLN	0.4 <= aval < 0.5	0.3 <= aval < 0.4	aval < 0.3
Chemistry	Phosphorus	Hyperphosphatemia	H	mmol/L	aval <= ULN	ULN < aval < 1.78	1.78 <= aval < 2.26	2.26 <= aval < 3.23	aval >= 3.23
Chemistry	Potassium	Hyperkalemia	H	mmol/L	aval <= ULN	ULN < aval <= 5.5	5.5 < aval <= 6	6 < aval <= 7	7 < aval
Chemistry	Potassium	Hypokalemia	L	mmol/L	LLN <= aval	3 <= aval < LLN		2.5 <= aval < 3	aval < 2.5
Chemistry	Sodium	Hypernatremia	H	mmol/L	aval <= ULN	ULN < aval <= 150	150 < aval <= 155	155 < aval <= 160	160 < aval
Chemistry	Sodium	Hyponatremia	L	mmol/L	LLN <= aval	130 <= aval < LLN	125 <= aval < 130	120 <= aval < 125	aval < 120

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Chemistry	Total Bilirubin	Blood bilirubin increased	H	umol/L	(upcase(bnrind) in ('NORMAL','LOW') and aval <= ULN) or (upcase(bnrind) ='HIGH' and aval <= base)	(upcase(bnrind) in ('NORMAL','LOW') and ULN < aval <= 1.5*ULN) or (upcase(bnrind) ='HIGH' and base<aval<=1.5*base)	(upcase(bnrind) in ('NORMAL','LOW') and 1.5*ULN < aval <= 3*ULN) or (upcase(bnrind) ='HIGH' and 1.5*base<aval<= 3*base)	(upcase(bnrind) in ('NORMAL','LOW') and 3*ULN < aval <= 10*ULN) or (upcase(bnrind) ='HIGH' and 3*base<aval<=10*base)	(upcase(bnrind) in ('NORMAL','LOW') and 10*ULN < aval) or (upcase(bnrind) ='HIGH' and 10*base<aval)
Chemistry	Bile Acid		NA						
Chemistry	Calcium		NA						
Chemistry	Creatinine								
Chemistry	Direct Bilirubin		NA						
Chemistry	Indirect Bilirubin		NA						
Chemistry	Protein		NA						
Chemistry	Uric Acid		NA						
Urinalysis	Acid Urate Crystals		NA						
Urinalysis	Amorphous Crystals		NA						
Urinalysis	Bacteria		NA						

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Urinalysis	Calcium Oxalate Crystals		NA						
Urinalysis	Casts		NA						
Urinalysis	Clarity		NA						
Urinalysis	Color		NA						
Urinalysis	Glucose		NA						
Urinalysis	Hyaline Casts		NA						
Urinalysis	Ketones		NA						
Urinalysis	LB Parameter - Urinalysis		NA						
Urinalysis	Leukocyte Cell Clumps		NA						
Urinalysis	Leukocyte Esterase		NA						
Urinalysis	Macroscopic Blood		NA						
Urinalysis	Microscopic Sediment Analysis		NA						
Urinalysis	Mucous Threads		NA						
Urinalysis	Nitrite		NA						
Urinalysis	pH		NA						
Urinalysis	RBC per HPF-CL		NA						

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Urinalysis	Renal Tubular Epithelial Cells		NA						
Urinalysis	Specific Gravity		NA						
Urinalysis	Squamous Epithelial Cells		NA						
Urinalysis	Transitional Epithelial Cells		NA						
Urinalysis	Urine Bilirubin		NA						
Urinalysis	Urine Erythrocytes		NA						
Urinalysis	Urine Leukocytes		NA						
Urinalysis	Urine Protein		NA						
Urinalysis	Urobilinogen		NA						
Urinalysis	WBC per HPF-CL		NA						
Pregnancy test	Choriogonadotropin Beta		NA						

Category	Parameter	CTCAE Term	CTC Grading direction: Hypo (L)/ Hyper (H)/ No Grading (NA)	CTC Lab Test Unit	CTC Grade 0	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Pregnancy test	Choriogonadotropin Beta Qualitative		NA						
Pregnancy test	Urine Choriogonadotropin Beta		NA						

10.3.4 Vital Signs

Vital signs parameters include:

- weight (kg)
- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- heart rate (beats/min)

Actual values and corresponding changes from baseline will be summarized by visit as descriptive statistics.

All vital signs data will be presented in a by-subject listing.

10.3.5 12-lead ECG

All ECGs will be sent to a local and central cardiology laboratory for reading and analysis. ECG measurement will include:

- RR, defined as the interval between 2 consecutive R waves (ms);
- Heart rate (HR, in beat per minute [bpm]), calculated as 60000 / RR (ms);
- P-R, defined as the interval between P and R waves (ms);
- QRS, defined as the distance between the Q and the S waves (ms);
- QT, defined as the interval between Q and T waves (ms);
- $QTcF\ (ms) = QT\ (ms) / RR\ (s)^{1/3}$.

The triplicate values will be averaged in order to obtain one single value per subject and time point.

As per Protocol Amendment Nº 2, central ECG reading will not be performed.

10.3.5.1 Central Tendency Analysis

Actual values for central assessment ECG parameters and their changes from baseline will be summarized using the descriptive statistics by time point. Ninety percent CIs of the mean will be presented as well. Standard deviation will be computed only if at least 3 records are available and 90% CIs only for cohorts in which at least 6 subjects are available.

Graphical representation of mean changes from baseline (with their 90% CIs upper bound when applicable) over time will be provided.

10.3.5.2 Categorical Analysis

The number and percentage of subjects presenting at least one value above the thresholds (irrespectively of the cycle or time point) as defined in Table 3 will be computed per cohort and overall. All ECG collected (including unscheduled assessments) will be used for this analysis.

Table 3 - Thresholds for categorical analysis and corresponding flags for listings

Criteria	Flag
Actual values	
P-R > 220 ms	H
QRS > 120 ms	H
QTcF interval > 450 ms	B

QTcF interval > 480 ms	H
QTcF interval > 500 ms	P
Changes from baseline	
P-R relative change > 25%	I
QRS relative changes > 25%	I
QTcF interval increase from baseline > 30 ms	I
QTcF interval increase from baseline > 60 ms	I+

Flagging system will be used in listings to identify values above thresholds, also not necessarily related to clinically significant events, the flags can be interpreted as follows:

- B: Borderline value;
- H: High value;
- P: Prolonged value;
- I: Noticeable absolute increase from baseline;
- I+: Marked absolute increase from baseline.

10.3.5.3 Morphological Analysis

A qualitative interpretation of the ECG will be performed by the cardiologist. This qualitative interpretation will provide a codification of the abnormalities detected on the recordings according to a code list grouping the abnormalities as:

- Q or Qs pattern;
- Axis and Voltage;
- Hypertrophy;
- ST depression and elevation;
- T/U wave abnormalities;
- AV conduction;
- Intraventricular conduction defects;
- Rhythm;
- Technical issue;
- Overall conclusion.

Number and percentage of subjects presenting at least one treatment emergent abnormality as defined by the code list will be computed per cohort and overall.

Treatment-emergent abnormality will be defined as any abnormality not already reported on the baseline ECG.

All treatment emergent abnormalities will be listed. Individual data listings will be displayed sorted by cohort, subject, and time-point, a flag will be added to identify values above thresholds as presented in Table 3.

10.3.6 Other Safety Analysis

ECOG PS will be presented as contingency tables by time point. Missing data will not be considered as a category and the calculation of frequencies will use the number of non-missing observations.

Any abnormal finding in ophthalmologic examination will be listed for each subject including the following: date of assessment, type of abnormality, whether the patient wears contact lenses, visual acuity and the results from left and right eye if available.

All safety data collected will be provided in by-subject listings.

10.3.7 Medications and procedures

Medications/Procedures will be classified into three categories:

- Prior: defined as medications/procedures with start date before the date of first administration of study drug.
- Concomitant: defined as medications/procedures administered during treatment period, between first and last administration of study drug.
- Post: defined as medications/procedures started after the date of last administration of study drug.

Details for handling of completely/partially missing dates are described in Section 8.1.2.

Prior and concomitant medications will be summarized by anatomical therapeutic chemical (ATC) levels 2, 4 and WHO drug preferred name. In case multiple ATC codes are assigned to a drug, all ATC-2nd level terms will be used for reporting.

In addition, a summary table will be provided describing:

- The number and percentage of subject with Sevelamer
- Time from treatment start to first administration of Sevelamer defined as date of start of Sevelamer use - date of first administration of the study drug +1. Missing day will be imputed as first day of month and missing month will be imputed as January. Completely missing date will not be imputed.
- Maximal dose of Sevelamer per subject
- The number and percentage of subject with Sevelamer, lanthanum carbonate and acetazolamide (Standardized term)

All medications and procedures date will also be listed.

Post-withdrawal anti-cancer treatments and any procedures will be listed and will include:

- Post-withdrawal radiotherapy: location, dose, start and end date, number of fraction days.
- Post-withdrawal anti-cancer therapy: therapy agent, therapy class, intent of therapy, line number, start and end date, reason for therapy.
- Procedures: procedure name/description, reason for procedure, if hospitalization was required, date of procedure.

[redacted]

[redacted]

10.5 Pharmacokinetics

10.5.1 Debio 1347 Plasma concentration

Individual Debio 1347 plasma concentrations will be listed by cohort, gender, subject, and relative time from dosing on PK population, values will be presented as collected.

Concentrations will be summarized by timepoint according to time window specified in Table 4. Concentrations derived from samples taken outside of this time window will be considered as unscheduled, hence excluded from descriptive analysis. However, the derivation of PK parameters will not exclude those unscheduled samples since the actual time of sampling will be used instead of the nominal time. Invalid PK measurements (e.g. due to subject vomiting on the same date after dosing, or to sample collected after treatment interruption or dosing reduction and therefore not reflecting steady-state) will be excluded from analyses and flagged in the data listing.

Table 4 - Protocol specified time window for PK plasma sampling

Cycle	**1**		**2**	
Time point/Day	**14**	**28**	**14**	**28**
Pre-dose	**● - 2 h**	**● -2 h**	**● -2 h**	**● -2 h**
1 h post-dose		**● ± 20 min**		
3 h post-dose		**● ± 30 min**		**● ± 30 min**
7 h post-dose		**● ± 30 min**		

The following plots will be presented by time point for trough levels (i.e. pre-dose on Cycle 1 Day 14 and Day 28, Cycle 2 Day 14 and Day 28), concentrations at Cycle 1 Day 28 and Cycle 2 Day 28 separately. Unscheduled samples will not be presented in the figures:

- Arithmetic means ± arithmetic standard deviations using linear/linear scales
- Geometric means and 68% prediction interval using log10/linear scales, where the 68% prediction interval is calculated as exp(meanlog +/- SDlog) where meanlog and SDlog are mean and standard deviation of log-transformed concentration values.

10.5.2 Debio 1347 Pharmacokinetics parameters

Based on sparse sample plasma concentrations, PK parameters (C_{trough}, AUCτ and any other PK parameters as deemed appropriate) will be derived by population PK data analysis using a nonlinear mixed-effects modelling approach. A Data Analysis Plan will be prepared for the dedicated population PK analysis and will be presented separately.

Individual plasma PK parameters will be presented in a by-subject listing, and summarized by cohort and overall using descriptive statistics.

If deemed appropriate depending on the safety and efficacy outcomes, covariate and exposure-response analyses may be conducted. [redacted]

[redacted]

[redacted]

[redacted]

10.6 C-QTcF analysis

If deemed appropriate depending on the safety and efficacy outcomes and data availability, an exposure-response (C-QTcF) analysis may be performed as described below.

Concentration-response relationship will be investigated for change from baseline in QTcF from central reading and Debio 1347 plasma concentrations.

This study did not include a placebo control and no run-in period with ECG recording before dosing with study drug. Therefore, placebo effects on QTcF could not be evaluated and accounted for.

10.6.1 Graphical Exploration:

In order to assess quality of QTcF correction before and after dosing the following figures will be provided:

- Scatter plot of QTcF versus RR at baseline with a regression line.
- Scatter plot of change from baseline for QTcF versus change from baseline in RR for values collected during Debio 1347 treatment periods with a regression line.

In both cases, the regression lines should tend toward a horizontal line, otherwise, a dependency still exists between QTcF and RR and a study specific QT correction (QTcSS) may be considered as the preferred dependent variable.

The following exploratory plots will also be performed before starting the modelling:

- Scatterplot of individual change from baseline for QTc values vs. time-matched concentrations including a nonparametric trend curve will be provided to assess the pattern of the relationship.
- Scatterplot of individual change from baseline for HR values vs. time-matched concentrations including a nonparametric trend curve will be provided to detect impact of the treatment on HR.

10.6.2 Model Development

The model development will start with the pre-specified mixed linear model as detailed in Garnett et al. (2017) considering the change from baseline in QTcF as dependent variable. In case of the graphical exploration suggests that Fridericia correction does not account for all RR variation, change from baseline in QTcSS will be used as a sensitivity analysis.

The fixed effect parameters of the pre-specified model will be the intercept, slope for Debio 1347 concentrations, influence of baseline (centered on mean) on the intercept. Subject specific random effects will be added on the intercept and slope parameters with an unstructured covariance matrix. In the case that the unstructured covariance matrix is not supported by the data, other simplified or reduced structures will be investigated (ex. variance components). As no placebo group is included in the study, no time factor will be included in the model to account for circadian variations.

Additive effects on the intercept may be investigated, e.g. the effect of intrinsic factors (such as demographic, pathophysiological, or PGx characteristics if deemed appropriate) or extrinsic factors (such as concomitant medications).

10.6.3 Model Evaluation

Goodness of fit plots will be provided, consisting of:

- Quantile-quantile plots of residuals;
- Concentrations versus residuals;
- Time and baseline versus residuals;
- Any marked bias in residual plots may suggest model misspecification. In addition, structural model hypothesis will be checked from graphical exploratory plots;
- The absence of effect on HR will be investigated from time course of change from baseline for HR;
- The hypothesis of direct relationship will be evaluated from the time course of change from baseline for QTcF by cohort. If the central tendency analysis allows to reject the hypothesis of QT/QTcF prolongation, hysteresis phenomenon will not be considered, otherwise, hysteresis will be investigated by visual inspection comparing time of peaks in change from baseline for QTcF and concentrations;
- The hypothesis of linear relationship between change from baseline for QTcF and concentrations will be evaluated from exploratory scatter plots, the goodness of fit plots and will be supported by testing a quadratic concentration term in the model.

In case of the linear relationship between change from baseline for QTcF and Debio 1347 concentrations cannot be accepted, an alternative model such as saturable model will be considered.

10.6.4 Display of Results and Decision Rules

Parameters estimated from the selected model will be presented with their standard error and 95% CI.

Predicted change from baseline for QTcF at C_{max} geometric mean will be presented with their 2-sided 90% CI and a graphical display of predicted change from baseline for QTcF over the concentration range collected during the study will be provided.

The impact of Debio 1347 on QT/QTc prolongation will be considered as below the threshold of regulatory concern if the upper bound of the 90% CI of predicted change from baseline for QTcF at C_{max} is below the regulatory limit of 20 milliseconds, which is generally applied for oncology compounds (Maison-Blanche et al. (2013), Sarapa and Britto (2008)).

[redacted]

10.8 Interim Analyses

10.8.1 Planned interim analysis

This study will have IDMC analyses as described in IDMC Charter with focus on study safety, drug tolerability as well as efficacy.

As a part of IDMCs, an interim analysis will be conducted at end of Stage 1 to assess ORR homogeneity across baskets as well as futility. The testing will be conducted as per the schema provided in Figure 1.

The interim analysis will be performed at end of Stage 1 on the first 27 evaluable subjects i.e. subjects in the ITT who have at least 1 post-baseline tumor assessments or progressed.

Every effort will be made to ensure equal accrual rates between cohorts during Stage 1. In case of unequal accrual rates during stage 1, the interim analysis will be conducted when the slowest enrolling cohort will have a minimum of 4 evaluable subjects and the study has a minimum of 27 evaluable subjects with a maximum of 13 evaluable subjects in any of the other cohorts.

A feasibility assessment will be evaluated prior to assessment of homogeneity to ensure the recruitment feasibility in the targeted population. One or more cohorts may be stopped prematurely as a result of the feasibility assessment. The homogeneity will be assessed by comparing, across cohort, the ORR as assessed locally by investigator at the time of the data cut-off. ORR to be used in the homogeneity assessment will be defined as the proportion of subject with a BOR of confirmed or unconfirmed CR or PR as locally assessed by the investigator. The BOR will be derived using all disease assessments performed locally by investigator prior to the data cut-off. The homogeneity assessment will be performed by comparing the observed p-value for the Fisher's exact test for 3x2 contingency tables to the pre-defined cut off value of 0.5. Homogeneity assumption will be rejected if the p-value generated is below 0.5. The cut-off value was determined as part of the simulations for sample size determination (see Section 6).

A futility assessment will be performed after the homogeneity assessment. Futility stopping rules are described in Table 5.

Table 5 - Futility stopping rules

Homogeneity assessment	**Futility assessment sample**	**Futility stopping rule**
Homogeneity met	All cohorts combined on first 27 evaluable subjects across cohorts	Stop study for futility if less than 3 responders If 3 or more responders, continue to Stage 2 and enroll the remaining subjects across all cohorts.
Homogeneity not met	First 9 evaluable subjects OR all evaluable subjects if cohort enrolled less than 9 subjects	Stop individual cohort for futility if 0 responder If 1 or more responders, cohort is eligible to continue into Stage 2.

Note: For homogeneity and futility assessment at the interim analysis, responder is defined as a subject with a BOR of confirmed or unconfirmed PR or CR based on investigator assessment.

In addition to the homogeneity and futility assessment procedure described above, the posterior probability of ORR≥15% in any of the cohorts will be provided to IDMC members as supportive information for their recommendation. Based on simulations, a cutoff of a posterior probability (of ORR≥15%) less than 65% (< 65%) in any of the cohorts, when used as a secondary assessment criteria for heterogeneity, provided improved operating characteristics (see Appendix in section 13.4). Posterior probability will be calculated using a uniform prior beta distribution with parameters 1 and 1.

If homogeneity is concluded at end of Stage 1, every effort will be made to ensure comparable enrolment rates between the three cohorts during Stage 2.

10.8.2 Data monitoring at the second IDMC meeting

Due to the slow accrual in cohort 2 (urothelial cancer), the above sample size criteria on timing of the interim analysis was not achieved and the planned interim analysis was not performed as planned.

The second IDMC meeting convened when the sample size in cohorts 1, 2, 3 were n=30, n=4, n=29, respectively and pooled total n=63. The homogeneity assessment (Fisher's exact test) was not performed. The estimated ORR unconfirmed by cohort and total subjects and by local and central reading is summarized in Table 6.

The results of this data monitoring review of pooled data showed that the antitumor activity of Debio 1347 was lower than initially assumed at the time the protocol was developed. Considering that further enrolment is unlikely to substantially change the magnitude of the efficacy observed up to now, Debiopharm decided to permanently halt the enrolment in the study after consultation with the IDMC on June 10th, 2020.

Table 6 - Objective Response Rate Unconfirmed (uORR) results observed at second IDMC

	Cohort 1 (Biliary Tract Cancer) (N=30)	Cohort 2 (Urothelial Cancer) (N=4)	Cohort 3 (All Other Solid Tumor Histologies) (N=29)	Total (N=63)	
Local reading uORR n(%)	4 (13.3)	0	0	4 (6.3)	
Central reading uORR n(%)	2 (6.7)	0	1 (3.4)	3 (4.8)	

11 MODIFICATION HISTORY

Version	Major changes from previous version
0.1	Not applicable, first draft version
1.0	- Subgroup analysis on subjects with and without dose-reduction. The aim is to explore the efficacy information while dose reduced. - Clarification and more detailed description of the analysis on section 10.1 and 10.3. - A supportive analysis with a censoring rule for PFS and DOR is added. This new censoring rule will assess the impact of censoring the subjects who initiate a new systemic therapy prior to progression. The aim is to add this analysis to cover the rare case where potentially one subject may initiate a new therapy prior to progression. Since the protocol require a follow-up until progression regardless of treatment status, a radiological assessment following a clinical progression to confirm the progression, this may limit the cases of drop-outs prior to progression. - The sentence "Subjects with a clinical progression determined by investigator will be scheduled to have a radiologic tumor assessment as per protocol. The response designation determined per RECIST criteria 1.1 using this scan will be included in the derivation of BOR. In case the planned scan is not performed, then the clinical progression will be used in the BOR derivation." is updated to remove the use of clinical progression as it is removed from protocol version 2. Indeed, the use of clinical progression does not impact any efficacy endpoint since PFS considers

	only documented progression. Therefore, clinical progression will be shown separately. - ECG population removed, as it is also removed in the protocol version 2. ECG analysis will be performed on Safety population rather than a dedicated ECG population. - Posterior probability added in Interim Analysis in order to provide to IDMC as additional information that could support their recommendation.
2.0	- Study design has been changed: No interim analysis performed during the 2nd IDMC meeting,…..

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13 APPENDICES

13.1 Reporting Conventions

The TLFs shells template will be provided in a separate document.

13.2 Listing of Tables, Figures and Listings

The TLFs shells template will be provided in a separate document.

13.4 Operation characteristics of additional decision criteria

13.4.1 Study design

13.4.1.1 Study design overview

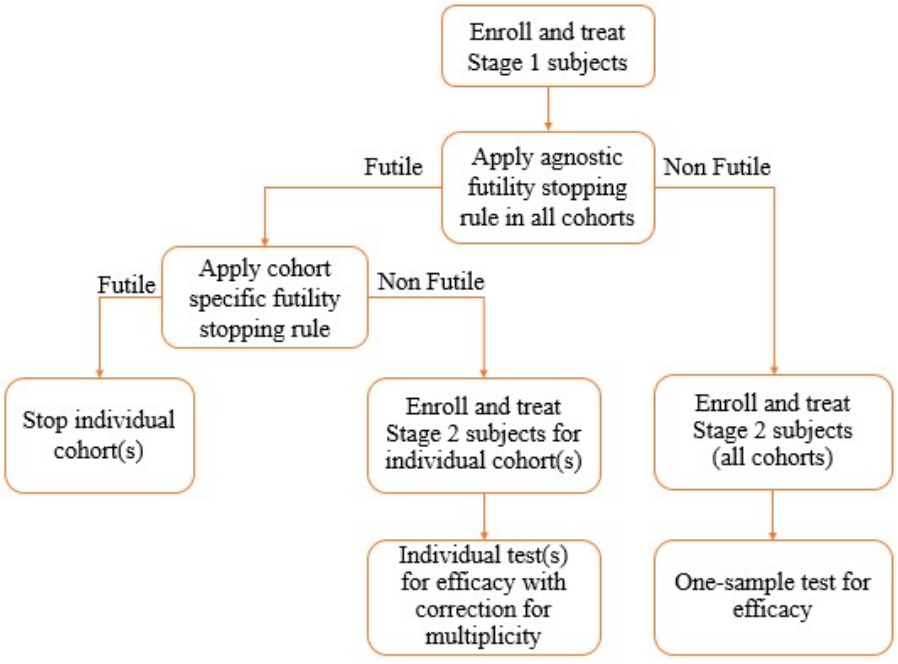
A basket two stage adaptive design will be used to assess the efficacy of Debio 1347 in terms of ORR. The study will include 3 cohorts of subjects comprising biliary tract cancer (Cohort 1), urothelial cancer (Cohort 2) and, in Cohort 3, all other solid tumor histologies not included in cohort 1 or cohort 2, such as non-small cell lung cancer (NSCLC), head and neck cancer, thyroid cancer, oral cancer, breast cancer, prostate cancer and others but excluding primary brain tumors.

An interim analysis will be conducted at end of Stage 1 to assess futility for agnostic approach and then a futility for each cohort if agnostic approach is not selected. The testing will be conducted as per the schema provided in Figure 2. This interim analysis will be performed at end of Stage 1 on the first 27 evaluable subjects, with a minimum 4 and a maximum of 13 evaluable subjects per cohort, i.e. subjects who have at least 1 post-baseline tumor assessments or progressed. In the case if for the first 27 evaluable subjects, the minimal number of subjects required is not reached in a cohort, then additional subjects will be included in this cohort to reach at least 4 subjects per cohort.

If overall futility for agnostic approach is not met, the next analysis steps will be conducted using combined data from all cohorts. If overall futility for agnostic approach is met, data will be analysed separately for each individual cohort and an additional futility will be conducted on each cohort. Table 7 shows the futility criteria in term of responders in each cohort.

Stage 1 will require 27 evaluable subjects across the three cohorts assuming an equal accrual rate per cohort. Stage 2 will require 86 evaluable subjects across all cohorts or per individual cohort depending on results of assessments scheduled at the end of Stage 1 (see Figure 2). The study design is an updated version of the Cunanan et al. (2017)).

Figure 2 - Graphical algorithm representing study design



13.4.1.2 Interim Decision criteria

At interim analysis, overall futility of agnostic approach will be first assessed in terms of ORR in all cohorts, defined as the proportion of subject with a BOR of confirmed or unconfirmed CR or PR as locally assessed by the investigator. The BOR will be derived using all disease assessments performed locally by investigator prior to the data cut-off. The overall futility for agnostic approach will be evaluated determined using two decision criteria (See Table 7).

Table 7 - Decision criteria for Overall futility for agnostic approach

Decision		Criteria 1 (Fisher & Posterior probability)	Criteria 2 (Posterior probability)
Overall futility for agnostic approach	Met (Do NOT continue with agnostic approach in stage2)	P-value of Fisher exact test ≤ 0.5 or P[ORR≥15%] < 65% in at least one cohort	P[ORR≥15%] < 65% in at least one cohort
	Not Met Continue with agnostic approach in stage 2	p-value of Fisher exact test > 0.5 and P[ORR≥15%] ≥ 65% in any of the cohorts	P[ORR≥15%] ≥ 65% in any of the cohorts

The posterior probability (denoted P) calculated using a uniform prior beta distribution Beta (1, 1) and with fisher exact test (for criteria 2). The fisher exact test consists of comparing the observed p-value for the Fisher's exact test for 3x2 contingency tables to the pre-defined cut off value of 0.5.

If overall futility for agnostic approach is not met, the next analysis steps will be conducted using combined data from all cohorts. If overall futility for agnostic approach is met, data will be analyzed separately for each individual cohort and an additional futility will be conducted on each cohort. An individual futility analysis will be conducted using the following stopping rule:

- Stop individual cohort for futility if 0 responder;
- If 1 or more responders, cohort is eligible to continue into Stage 2.

13.4.1.3 Operation characteristics

In the setting of multiple cohorts, there is no clear analog of the conventional type 1 and type 2 error rates. The null scenario is considered as the case when the drug does not work in any of the cohorts. However, there is a composite of alternative scenarios that are considered simultaneously, such as that the drug may only work in one cohorts, or that it works in two cohorts, and so on.

The following three metrics are used to construct our proposed design and evaluate its performance under various scenarios: FWER, Marginal power, and expected trial sample size (EN).

The FWER is defined as the probability of incorrectly declaring activity in one or more baskets when in fact the drug does not work in any cohort.

The marginal power for a cohort is defined as the probability of correctly declaring activity in cohort k when in fact the drug works in cohort k. The marginal power differs depending on the true alternative, that is, the number of cohorts in which the drug actually works.

The selection an optimal design involves first electing all candidate designs for which both the FWER and the marginal power for a specific alternative conform to desired levels, then choosing from these candidates the design that optimizes a utility function that trades off power and expected sample size across all alternative hypotheses. If no candidate designs satisfy the condition on both FWER and marginal power, then the candidate designs will be determined using FWER.

13.4.2 Simulation study

Data for multiple studies will be generated using simulations to derive the operation characteristics of the proposed design. The simulation will be performed for various numbers of active cohorts (i.e. 0, 1, 2 and 3 active cohorts). A total of 100000 simulated studies were used to generate the proposed study design and the operation characteristics under the assumption of 0, 1, 2 and 3 active cohorts. The detail of the simulation are described below.

13.4.2.1 Simulate a study

For each simulated study, the sample size at stage 1 is set to 27 subjects with 4 to 13 per cohort. An inactive ORR is set at 15% and an active ORR is set at 30%. The subjects and time of enrolment are simulated using exponential distribution. The first 27 subjects in any cohort with the smallest time of enrolment will be selected. If among the first 27 subjects, the minimum number of subjects per cohort is not met in one cohort, then additional subjects will be enrolled in this cohort to reach this requirement.

The interim decision criteria will be evaluated on the number of subjects included in interim analysis and the simulated number of responders and the corresponding posterior distribution. The number of responders are simulated using binomial distribution and the pre-specified ORR in each cohort. With a prior beta distribution Beta(1,1), the conjugate posterior distribution of ORR in each cohort is defined as a beta distribution

Beta(1 + number of responders, 1+ number of non-responders).

If the agnostic approach is not rejected, the subjects will be enrolled into 3 cohorts in the stage 2 with a minimal of 1 and up to 45 subjects per cohorts, there will be on average 30 subjects per cohort under an equal accrual rate. A maximum of 90 subjects will be enrolled in stage 2. Combining the responders observed in the study, an exact binomial test comparing the observed ORR against the inactive ORR will be performed at a one-sided alpha level of 5%.

If the agnostic approach is rejected, then the futility in each cohort will be evaluated on the numbers of responders. For any cohort where futility criteria is not met, a number of subjects N21, which is the parameter in the simulation, will be enrolled in stage 2. Combining the responders observed in stage 1 and in stage 2 in each non-futile cohort, an exact binomial test comparing the observed ORR against the inactive ORR will be performed in each basket separately at a one-sided alpha level of 5%/ number of non-futile basket.

13.4.3 Estimation of FWER and Marginal Power

The trial design will be simulated 100000 times in order to gain sufficient data to calculate the measures below:

- Power: Probability of rejecting 15% in each cohort or in all cohorts combined.
- FWER: Probability of H0 in any inactive cohort or in all cohorts combined.
- % of heterogeneity: Probability of heterogeneity case
- Non-Futility: Probability of stopping in each cohort or stop the study
- Expected Sample Size:

$$EN = \sum_{k=1}^{K} n_{1k} + \sum_{k \in K^{\star}} n_{2k} \Pr(r_{Sk} \geqslant 1 | \text{heterogeneous design path}) \Pr(\text{heterogeneous design path}) + N_2 \Pr(r_C \geqslant 5 | \text{homogeneous design path}) \Pr(\text{homogeneous design path})$$

13.5 Operation characteristics

The operation characteristics are calculated using simulations with 27 evaluable subjects in Stage 1 and 86 evaluable subjects in Stage 2 in each cohort

Sample size and design operating characteristics are presented in Table 8 for criteria 1 using fisher exact test and posterior probability and in Table 9 for criteria 2 using posterior probability only.

Table 8 - Power and expected sample size based on 100000 simulations using criteria 1 (Fisher & Posterior probability)

Assumed ORR of 15% for inactive cohorts and 30% for active cohorts	**Number of truly active cohorts**			
	0 Active	**1 Active**	**2 Active**	**3 Active**
Marginal Power				
FWER	5.0%	10.0%	21.6%	NA
Power 1 active cohort	2.4%	84.0%	87.8%	90.5%
Power 2 active cohorts	2.4%	9.0%	88.0%	90.5%
Power 3 active cohorts	2.3%	9.0%	21.6%	90.7%
Expected sample size	202	207	202	181
% Futility for agnostic met at end of stage 1	91.3%	86.3%	77.1%	58.3%
Cohort 1 continuing to stage 2	67.6%	81.8%	72.5%	53.6%
Cohort 2 continuing to stage 2	67.8%	62.9%	72.5%	53.6%
Cohort 3 continuing to stage 2	67.5%	62.6%	53.2%	53.8%
% Futility for agnostic not met at end of stage 1	8.7%	13.7%	22.9%	41.7%
Continuing to stage 2	8.7%	13.7%	22.9%	41.7%

Table 9 - Power and expected sample size based on 100000 simulations using criteria 2 (Posterior probability only)

Assumed ORR of 15% for inactive cohorts and 30% for active cohorts	**Number of truly active cohorts**			
	0 Active	**1 Active**	**2 Active**	**3 Active**
Marginal Power				
FWER	5.0%	12.2%	29.3%	NA
Power 1 active cohort	2.4%	83.1%	88.3%	91.5%
Power 2 active cohorts	2.5%	11.2%	88.2%	91.5%
Power 3 active cohorts	2.5%	11.2%	29.3%	91.6%
Expected sample size	201	199	186	156
% Futility for agnostic met at end of stage 1	90.8%	83.2%	69.2%	43.3%
Cohort 1 continuing to stage 2	67.2%	78.6%	64.7%	38.8%
Cohort 2 continuing to stage 2	67.0%	59.5%	64.6%	38.7%

Cohort 3 continuing to stage 2	67.0%	59.5%	45.5%	38.7%
% Futility for agnostic not met at end of stage 1	9.2%	16.8%	30.8%	56.7%
Continuing to stage 2	9.2%	16.8%	30.8%	56.7%

13.6 Criteria of protocol violation that can lead to exclusion from the Per Protocol populations

Criteria of protocol violation that can lead to exclusion from MTD or Efficacy populations	Per Protocol	Exception listing #
Inclusion Criteria		
1. Written informed consent given according to International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines and local regulations.		
2. Cytologically or histologically confirmed advanced solid tumor.		
3. Radiographic progression on prior systemic therapy; prior localized therapy (i.e., radiation, ablation, embolization) is allowed provided radiographic progression out-of-field or in the treatment field is shown.		
4. Male or female ≥18 years of age.		
5. Locally-advanced (unresectable) or metastatic disease harboring an FGFR1-3 gene fusion/rearrangement potentially leading to a functional FGFR aberrant protein, identified through local and/or central molecular assay.		

a) The subject must have received at least one prior line of standard therapy appropriate for their tumor type and stage of disease (if available), and, in the opinion of the Investigator, s/he would have been unlikely to tolerate or derive clinically meaningful benefit from further appropriate standard of care therapy. In particular: a. Biliary tract cancer subjects must have progressed on/after gemcitabine-based chemotherapy (including subjects who progressed within 6 months of gemtabicine-based adjuvant chemotherapy). Subjects can have received additional chemotherapy after documented intolerance to gemcitabine. b. Urothelial cancer subjects must have progressed on/after cisplatin-based or carboplatin based chemotherapy either given for advanced disease or within 12 months from completion if given as neoadjuvant or adjuvant therapy and anti-PD1/PDL1 therapy (unless not available, contraindicated for some reasons or refused by the subject). c. NSCLC subjects must have progressed on chemotherapy and anti PD1/PDL1 therapy (unless contraindicated for some reasons). Subjects with known EGFR mutations, ALK rearrangement or BRAF V600E mutation must have received the relevant target therapy (unless not available). d. For all other tumor types, subjects must have progressed on/after appropriate standard of care (SOC) therapy (evidence-based level 1). Subjects who harbor genomic aberrations for which approved target therapy is available must have received such therapy. HER2+ or ER/PR+ breast cancer subjects should have received at least one line of HER2-targeted or ER-targeted, respectively.		
7. Measurable disease according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1.		
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1.		

9. Screening laboratory values as follows: a. Absolute neutrophil count (ANC) ≥ 1,000/mm3 [1.0 x 109/L]. b. Platelet count ≥ 75,000/mm3 [75 x 109/L]. c. Hemoglobin ≥ 8.0 g/dL. d. Total bilirubin ≤ 2 x upper normal limit (UNL) [biliary stent allowed]. A subject with an isolated elevation of indirect bilirubin is eligible. e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x UNL (5 x UNL in the presence of liver metastases). f. Calculated or measured creatinine clearance ≥ 30 mL/min (creatinine clearance measured based on 24-hour urine collection should be considered to help assess eligibility). g. Serum phosphate < 1.5 x UNL.		

10. Female subjects of child-bearing potential must have a negative serum pregnancy test (minimum sensitivity of 25 mIU/mL) at screening and be willing to practice the highly effective contraception methods listed below from the time of study entry up to 6 months after the last day of treatment: a. Intrauterine device (IUD) b. Intrauterine hormone-releasing system (IUS) c. Bilateral tubal occlusion d. Vasectomized partner e. Sexual abstinence if corresponds to usual and preferred lifestyle of subject. For hormonal contraceptives . Of note: - Female subjects of non-childbearing potential are defined as either pre-menopausal with a documented tubal ligation or hysterectomy or post-menopausal with 12 months of spontaneous amenorrhea. - Female subjects of child-bearing potential must refrain from donating egg(s) during the clinical study and for 6 months after Debio 1347 discontinuation. - Male subjects must agree to use a condom from study entry and up to 6 months after the last day of treatment. The subject's female partner should use highly effective contraception methods, which may include hormonal contraceptives or any of the methods outlined above, during this period. - Male subjects must refrain from donating sperm during the clinical study and for 6 months after Debio 1347 discontinuation.		
11. Available fresh tumor sample (preferably) or, if no fresh sample can be obtained, archived tumor sample (slides or block) for central analysis of FGFR status or retrospective central confirmation in case of local screening.		
12. Life expectancy ≥ 3 months.		
Exclusion Criteria		

1. History of hypersensitivity to any of the excipients in the Debio 1347 formulation (lactose hydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate and magnesium stearate).		
2. Prior treatment with a FGFR1-3 selective inhibitor.		
3. History and/or current evidence of ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, myocardia, or lung, excepting calcified lymph nodes, lung nodules and asymptomatic vascular or cartilage/tendon calcifications.		
4. Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination.		
5. Chemotherapy, radiotherapy or small molecule anti-cancer agents within 2 weeks prior to initial dosing with Debio 1347 (3 weeks for immune checkpoint inhibitors).		
6. Administration of any investigational agent within 2 weeks prior to initial dosing with Debio 1347 (3 weeks for immune checkpoint inhibitors).		
7. Surgery requiring general anesthesia, except diagnostic biopsy or local procedure, within 3 weeks prior to initial dosing with Debio 1347 and/or if the subject has not fully recovered from the surgery.		
8. Grade > 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0) AEs or toxicities from previous treatments except: a. Albumin (≥ 2.5 g/dL is allowed). b. AST and ALT in subjects with liver metastases (£ 5 × ULN is allowed). c. Alkaline phosphatase (ALP) in subjects with bone metastases (£ 5 × ULN is allowed). d. Any grade of alopecia is allowed. e. Other Grade 1-2 clinically insignificant laboratory abnormalities are allowed.		

9. Symptomatic or unstable brain metastases < 1 month (**Of note**: Subjects with asymptomatic stable and treated brain metastases are eligible).		
10. Total corrected and/or ionized serum calcium ≥ 1.5 x UNL (corrected calcium = [0.8 x (normal albumin - subject albumin)] + serum calcium level).		
11. Gastro-intestinal disorders that could affect drug absorption (including, but not limited to, gastric resection, significant bowel obstruction, active ulcerative colitis, active Crohn's disease).		
12. Concomitant treatment with a prohibited medication.		
13. Subjects with a known history of uncontrolled or unstable angina or myocardial infarction within the last 6 months, unstable cardiac arrhythmias despite treatment (*subjects with a history of atrial fibrillation stabilized under treatment are allowed*), unexplained recurrent syncope, family history of sudden death from cardiac-related causes, congestive heart failure greater than New York Heart Association (NYHA) class II, uncontrolled diabetes, uncontrolled psychiatric disorders, severe ongoing infections or any other medical condition that might be aggravated by the treatment on evaluation.		
14. Prolongation of QTcF interval to greater than 480 msec.		
15. History of congenital long QT syndrome		
16. History of another malignancy other than the primary tumor within the last 2 years, with the exception of completely resected basal or squamous cell skin cancer or any successfully treated in-situ carcinoma, or clinically insignificant prostate cancer without any treatment intent (either treated or on active surveillance/watchful waiting). Other cancers within the last 2 years that are considered clinically insignificant by the treating physician should be discussed with the study Sponsor to assess eligibility.		
17. Known infection requiring the systemic use of, for example, an antibiotic or antiviral agent.		

18. Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.		
19. If female, pregnant or breast feeding.		
20. Unable to swallow and retain oral medications.		
21. Known contraindication to enhanced magnetic resonance imaging (MRI) and/or computerised tomography (CT) scan.		
Additional criteria		
Actual cumulative dose below 75% of planned cumulative dose from date of first dose to date of end of cycle 4 or date of treatment discontinuation, whichever occurs first;		
Major protocol deviations that may have an impact on efficacy endpoints.		

13.7 Study plan

Table 10 Study Plan (not applicable for subjects with Debio 1347 treatment ongoing after the implementation of Protocol Amendment N° 2)

	Pre-screening	Screening	Treatment										EOT/ Progression	Follow-up[n]
Cycle			1				2			3+				
Day		-28 to -1	1	8	14	28	1	14	28	1	14	28		
Window				±2	±2	-3	NO VISIT	±2	-3	NO VISIT	NO VISIT	-3		
Written informed consent for pre-screening (if applicable)[a]	●													
Pre-screening assessment of tumor FGFR fusion/rearrangement[a]	●													
Written informed consent for study		●												
Review eligibility criteria		●												
Demographics, medical history, height		●												
Physical examination, weight		●	●		●	●		●	●			●	●	
Vital signs, ECOG PS[b]		●	●		●	●		●	●			●	●	
Triplicate 12-lead ECG[c] (for windows see footnote)		●	●			●			●			●	●	
Hematology, fasting biochemistry[d]		●	●	■[d]	●	●		●	●			●	●	
Serum pregnancy test (minimum sensitivity of 25 mIU/mL) if applicable		●												
Urinary pregnancy test[e]			●			●			●			●	●	●[n]
Urinalysis[e]		●	●			●			●			●	●	
Ophtalmological test[l]		●											●	
Tumour staging		●												
CT scan/MRI, RECIST 1.1 tumor assessment[f]		●							●			●[f]	●	●[n]
Debio 1347 treatment				Once daily from Day 1 to Day 28 in each 28-day cycle										
[redacted]														
Blood sampling PK[g] (for windows see footnote)					●[g]	●[g]		●[g]	●[g]					
[redacted]														

[redacted]														
Tumour biopsy[k]		●[k]											●[k]	
Concomitant medications		→												→
Adverse events		→												→[n]
Survival														●[n]

Abbreviations: CT, computerised tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end-of-treatment; MRI, magnetic resonance imaging; [redacted];
PK, pharmacokinetics; PS, performance status.

a) Pre-screening for tumor FGFR fusion/rearrangement will be made either locally at the study site in a certified laboratory or in a central laboratory using RNA or DNA-based NGS techniques prior to or during the 28-day screening period. Only subjects harboring FGFR fusions/rearrangements potentially leading to a functional FGFR aberrant protein may undergo the complete clinical screening required for study participation. The test will be made on adequate fresh tumor tissue slides (preferably) or, only if not possible, adequate unstained archival slides or tumor block.

   Of note: A "liquid biopsy", e.g., ctDNA based test is acceptable for subject eligibility but then a pre-study treatment tissue sample is required for post-hoc confirmation of the fusion (see inclusion criterion No. 11 in Section **Error! Reference source not found.**).

   Of note: Written informed consent for pre-screening will be obtained only from subjects who require a central assessment of FGFR status.

b) BP and pulse rate will be taken after at least 5 minutes of supine rest.

c) Triplicate 12-lead ECGs (PR, RR, QRS and QTcF intervals) will be recorded after at least 5 minutes of supine rest at the following time points: Screening, pre-dose **Cycle 1** Day 1, pre-dose and 1, 3 and 7 hours post-dose **Cycle 1** Day 28, pre-dose and 3 hours post-dose **Cycle 2** Day 28, **in all subsequent cycles** at any time on Day 28 and at the time of disease progression and/or EOT.

   Of note: All ECGs will be sent to a central cardiology laboratory for reading and analysis.

   Of note: On Day 28 of Cycles 1 and 2, ECGs should be recorded maximum 20 min before each PK sample (see footnote g) below for PK sampling windows).

d) Hematology: Complete blood count with differential (including ANC), hemoglobin, platelet count.

   Of note: The screening sample can be combined with the pre-dose Day 1 sample if performed within 2 weeks prior to treatment start.

   Chemistry **FASTING**: Total protein, albumin, indirect and total bilirubin, AST, ALT, ALP, electrolytes (sodium, potassium, calcium, magnesium), serum phosphate, serum creatinine, creatinine clearance, uric acid, bile salts. **On Cycle 1 Day 8**: Only serum phosphate. The assessment can be performed in a local laboratory.

   Of note: The screening sample can be combined with the pre-dose Day 1 sample if performed within 2 weeks prior to treatment start.

Note regarding safety laboratory assessments: In the case of a significant laboratory abnormality or clinical or laboratory evidence of toxicity, the Investigator will collect additional samples for repeat or additional analyses at appropriate intervals. The subject will be closely followed until sufficient information has been obtained to determine the cause of the abnormality or the value has returned to an acceptable level. Appropriate remedial measures should be taken and the response recorded. Any clinically relevant change from baseline onwards must be recorded on the AE page of the eCRF.

e) Urinalysis: Red blood cells/hpf, white blood cells/hpf, casts/hpf and protein...

Urinary pregnancy test: Same time points as urinalysis up to EOT/progression, except at screening (done in serum). Urinary pregnancy test post-EOT: See item n) below. **Of note**: Urinary pregnancy test at baseline (**Cycle 1** Day 1) **to be done pre-dose.**

f) A CT scan/MRI and tumour assessment will be performed at the end of **Cycles** 2, 4 and 6 followed by every 3 cycles (end of cycle) for up to 24 months. In the case of response, imaging will be repeated 4 (± 3 days) weeks later. A CT scan/MRI and tumour assessment will be also be performed at the time of disease progression and/or EOT.

Of note: The radiological method will depend on site feasibility. For each subject, the same radiological method must be used throughout the study.

g) Blood samples for Debio 1347 PK will be collected as follows: Pre-dose **Cycle 1** Day 14; pre-dose and 1, 3 and 7 hours post-dose **Cycle 1** Day 28; pre-dose **Cycle 2** Day 14; pre-dose and 3 hours post-dose on **Cycle 2** Day 28. The exact date/time of Debio 1347 administration and PK sample collection will be recorded. Sampling windows are shown in the table below.

Of note: On Day 28 of Cycles 1 and 2, ECGs should be recorded **maximum 20 min before each PK sample**.

Cycle	**1**		**2**	
Time point/Day	**14**	**28**	**14**	**28**
Pre-dose	● - 2 h	● - 2 h	● -2 h	● - 2 h
1 h post-dose		● ± 20 min		
3 h post-dose		● ± 30 min		● ± 30 min
7 h post-dose		● ± 30 min		

[redacted]

Of note: These samples can be taken concurrently with the PK samples.

[redacted]

Of note: These samples can be taken concurrently with the PK samples.

k) A tumour biopsy will be collected a) at pre-screening/screening (necessary for inclusion and assessment of biomarkers pre-treatment [if biopsy not possible adequate unstained archival slides or tumor block must be made available]) and b) at disease progression whenever feasible. As per Protocol Amendment N 2, no further tumour biospies will be collected at time of progression.

l) The examination will be interpreted by a qualified ophthalmologist, including visual acuity testing, slit-lamp ophthalmoscopy and indirect ophthalmoscopy. At the EOT visit, only slit lamp ophthalmoscopy will be performed.

[redacted]

n) After treatment discontinuation (= EOT visit) subjects will be followed-up for:

1) Safety (AEs/SAEs) for 30 days from the date of the last Debio 1347 dose. After this period, the Investigator should report to the Sponsor any unusual safety information or any safety information that appears to be related to the study drug.

2) Survival every 12 weeks (± 14 days) from the date of the last Debio 1347 dose until death or loss to follow-up but no longer than for a total of 2 years after the last subject discontinued treatment.

3) Disease status only in subjects without PD every 12 weeks (± 14 days) from the date of the last Debio 1347 dose until PD, death or loss to follow-up but no longer than for a total of 2 years after the last subject discontinued treatment.

[redacted]

5) Urinary pregnancy test post-EOT: Every 28 days for 6 months (home pregnancy test is acceptable). All pregnancies detected during the 6-month post-EOT follow up period should be reported according to the standard process described in Section **Error! Reference source not found.**

Table 11 Study Plan (applicable to subjects with Debio 1347 treatment ongoing after the implementation of Protocol Amendment Nº 2)

	Ongoing Treatment*	EOT	EOS (30 days after last study drug intake)
Cycle	**any**		
Written informed consent (amendment N 2)	●		
Physical examination	●	●	●
Vital signs	●	●	●
ECG[a]	●	●	
Hematology, fasting biochemistry[b]	●	●	●
Urinary pregnancy test	●	●	●
Urinalysis	●	●	●
Adverse events[c]	●	●	●

*For all subjects with Debio 1347 treatment ongoing and who consented to participate in the study after the date of implementation of Protocol Amendment N 2, the assessments and procedures plan defined in the study protocol will no longer be in force and will be replaced by standard institutional care practice (at least every 2 months)

a) ECG trace (PR, RR, QRS and QTcF intervals) will be recorded after at least 5 minutes of supine rest.

b) Hematology: Complete blood count with differential (including ANC), hemoglobin, platelet count.

Chemistry: Total protein, albumin, indirect and total bilirubin, AST, ALT, ALP, electrolytes (sodium, potassium, calcium, magnesium), serum phosphate, serum creatinine, creatinine clearance. The assessment will be performed in a local laboratory.

Note regarding safety laboratory asessments: In case of a significant laboratory abnormality or clinical or laboratory evidence of toxicity, the Investigator will collect additional samples for repeat or additional analyses at appropriate intervals. The subject will be closely followed until sufficient information has been obtained to determine the cause of the abnormality or the value has returned to an acceptable level. Appropriate remedial measures should be taken, and the response recorded. Any clinically relevant change from baseline onwards must be recorded on the AE page of the eCRF.

c) AEs, AESI, SAEs must be documented in the study eCRF and in the dedicated report forms as specified in section 9.2 of this protocol.