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

NCT Number: NCT03834220

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STUDY PROTOCOL

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 FUZE Clinical Trial"

Clinical Development Phase: II

Investigational Medicinal Product: Debio 1347

EudraCT number: 2018-003584-53

IND number: 118244

Debiopharm International SA Study Number: Debio 1347-201

SPONSOR:
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Protocol version N° 3 dated 16 July 2020 integrating amendment Nº 1 & 2

Study Sponsor:	Debiopharm International SA, Ch. Messidor 5-7, P.O. Box 5911, CH-100 Lausanne, Switzerland
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The information in this protocol is confidential. It is provided to every potential Investigator and his/her team, as well as to the Independent Ethical Committee or Institutional Review Board, that must statute on the trial. No information can be provided to a third party without the written agreement of Debiopharm International SA, except for the medical personnel directly concerned by the trial and for the information needed by the subject and his/her family.

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STUDY SYNOPSIS

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 NUMBER	Debio 1347-201	**STUDY PHASE**	II
STUDY DESIGN	Multicentre, basket, two stage, adaptive single arm Phase II study in subjects with solid tumors harboring FGFR1-3 gene fusion/rearrangement. Three cohorts will be included consisting of subjects with biliary tract cancer (Cohort 1), urothelial cancer (Cohort 2) and all other solid tumor histologies not included in Cohorts 1-2 such as NSCLC, head and neck cancer, thyroid cancer, oral cancer, breast cancer, prostate cancer and others but excluding primary brain tumors (Cohort 3).		
STUDY OBJECTIVES	**Primary objective** To assess the efficacy of Debio 1347 in terms of ORR in subjects with solid tumors harboring FGFR1-3 gene fusion/rearrangement. **Secondary objectives** 1. To evaluate the efficacy of Debio 1347 in terms of DoR, DCR, PFS and OS. 2. To assess the safety of Debio 1347. 3. To assess exposure-response relationships vs efficacy and safety (notably QTcF). [redacted]		
ENDPOINTS	**Primary endpoint** ORR (defined as the proportion of subjects with a BOR of partial or complete response) as centrally measured by RECIST 1.1 criteria. **Secondary endpoints** 1. DoR (defined as the time from the date of the initial partial or complete response to date of the first documented progression or death due to any cause). 2. DCR (defined as the proportion of subjects with a BOR of CR or PR or SD). 3. PFS (defined as the time from the start date of treatment to date of the first documented progression 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 TEAEs assessed by NCI-CTCAE v5.0 and SAEs. 6. Debio 1347 plasma exposure (C_{trough}, 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 ECG and PK matching time-points. [redacted]		
STUDY POPULATION	Subjects with locally advanced (unresectable) or metastatic tumors with FGFR1-3 gene fusion/rearrangement who require systemic therapy and who have radiologic and/or clinical progression following at least one prior standard treatment or who have no satisfactory alternative		

	treatment options will be included in this study. Approximately 125 males or females ≥ 18 years will be recruited in North America, EU, the Middle East, South America and the Asia Pacific region.
INCLUSION CRITERIA	1. Written informed consent given according to ICH/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. 6. The subject must have received at least one prior line of standard therapy appropriate for 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 patient). 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 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 RECIST criteria version 1.1. 8. ECOG PS of 0 to 1. 9. Screening laboratory values as follows: a. ANC ≥ 1,000/mm3 [1.0 x 10^9/L]. b. Platelet count ≥ 75,000/mm^3 [75 x 10^9/L]. c. Hemoglobin ≥ 8.0 g/dL. d. Total bilirubin ≤ 2 x UNL [biliary stent allowed]. A subject with an isolated elevation of indirect bilirubin is eligible. e. AST and 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. IUD b. IUS c. Bilateral tubal occlusion d. Vasectomized partner e. Sexual abstinence if corresponds to usual and preferred lifestyle of subject. For hormonal contraceptives see Section 7.7.1 **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. **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. 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 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. 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 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 MRI and/or CT scan.
INVESTIGATIONAL MEDICINAL PRODUCT	Debio 1347 formulated as 20 mg tablets for oral administration.

TREATMENT DURATION	Subjects will be treated with Debio 1347 daily in 28-day cycles until the occurrence of disease progression (clinical or radiologic) or unacceptable toxicity (other treatment discontinuation criteria are described in Section 8.4.1).
PARTICIPANT DURATION	See above.
STUDY VISITS	Subjects will attend a pre-secreening visit (only those who undergo central assessment of FGFR status), a screening visit, a variable number of on-treatment visits depending on the number of treatment cycles, an EOT visit and a variable number of follow-up visits/contacts. For all subjects who will remain on treatment with Debio 1347 after the implementation of Protocol Amendment Nº 2, the assessments and procedures defined in the study protocol will no longer be in force and will be replaced by standard institutional care practice. Subects must be followed regularly (at least every 2 months) to assess the potential occurrence of safety events, as described in the Table 8.1b.
STUDY PERIOD/DURATION	18 months = estimated period and time in months from FPFV (first patient first visit) to LPLV (last patient last visit). As of the implementation date of Protocol Amendment Nº 2, subjects showing clinical benefit may continue treatment with Debio 1347 until a condition to stop treatment is met. The LPLV (last patient last visit) will occur 30 days after the end of treatment (EOT) for the last subject in the study.
STATISTICAL METHODS	**Sample size** A basket two stage adaptive design will be used to assess the efficacy of Debio 1347 in terms of ORR. 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. Assuming homogeneity across baskets and a 10% drop out the study would enroll approximately 125 subjects. 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 the study after consultation with the DMC on June 10th, 2020. **Randomisation** Not applicable. **Interim analysis** 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 basket and a maximum of 13 subjects per basket will be required for the end of Stage 1 analysis. ORR homogeneity will be assessed using a pre-defined cut-off for the critical value of the exact test for contingency tables. If homogeneity is declared, the next analysis steps will be conducted using combined data from all baskets; if heterogeneity is declared, data will be analyzed separately for each individual basket. The interim analysis at end of Stage 1 will be conducted by the DMC. Details on the roles and responsibilities of the DMC will be provided in the DMC charter. Based on initial review and monitoring of efficacy data, the interim analysis is cancelled. Efficacy analysis The ITT population will be the primary analysis population for efficacy analysis. Efficacy analyses will be repeated on the mITT population and the PP population as supportive analyses. The efficacy analysis will be conducted using centrally measured response as primary analysis and repeated on locally measured response as sensitivity analysis. The statistical testing for primary analysis will be conducted on ORR as centrally measured using a one-sided exact binomial test. The hypothesis tested will be: • Scenario 1: If the ORR homogeneity assumption is met at the interim analysis, then the hypothesis will be *H0: ORR ≤ 15% against H1: ORR > 15 % at alpha level of 5%* • Scenario 2: If the ORR homogeneity assumption is not met at the interim analysis, then a decision will be made at the time of interim analysis to further continue the study with only 1 cohort or 2 cohorts. Then the hypothesis tested at final stage will be. *H0: ORR ≤ 15% against H1: ORR > 15 % in each chosen cohort*

- Scenario 2a: In the case 1 cohort has been selected the statistical comparison will be conducted at an alpha level of 5%.
- Scenario 2b: In the case 2 cohorts have been selected the statistical comparison will be conducted at a Bonferroni adjusted alpha level of 2.5% for each cohort.

ORR, DCR and BOR will be summarized using frequencies and percentages. Confidence intervals will be presented overall and by cohort. DoR, PFS and OS will be analysed using the Kaplan Meier method.

Safety analysis

AEs: Treatment-emergent adverse events, TEAEs related to study drug, TEAEs by severity, TEAEs leading to treatment discontinuation and SAEs will be tabulated and listed by MedDRA system organ class and preferred term. All on study deaths and reasons will be listed.

Laboratory parameters: Safety laboratory parameters and corresponding changes from baseline will be presented as descriptive statistics by cohort and by timepoint. Shift tables will be produced.

ECGs: 12-lead ECG parameters and corresponding changes from baseline will be summarized by cohort and by visit as descriptive statistics. No central reading of the original ECGs will be performed. Central tendency, categorical and morphological analyses will be performed for all available parameters. Subordinated to the safety and efficacy outcome and data availability, an exposure-response (C-QTcF) analysis may be performed by linear mixed effect modeling based on ECG and PK matching time-points, if deemed appropriate.

Pharmacokinetic analysis

Individual Debio 1347 concentrations will be listed by gender, subject and time point. Graphic displays of plasma concentration vs time will be presented individually by subject, arithmetic means and geometric means. Pharmacokinetic parameters will be listed by subject and summarized by cohort and overall, as descriptive statistics and will be derived by population PK data analysis using a nonlinear mixed-effects modeling approach. If deemed appropriate, based on safety and efficacy outcome, relationships between exposure vs efficacy and safety may be evaluated. [redacted]

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUCτ	Area under the plasma concentration-time curve over the dosing interval τ
BOR	Best overall response
BP	Blood pressure
[redacted]	[redacted]
CI	Confidence interval
C_{max}	Maximum concentration
CoA	Certificate of analysis
CR	Complete response
CRO	Clinical research organisation
CSR	Clinical study report
CT	Computerised tomography
[redacted]	[redacted]
C_{trough}	Trough concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DMC	Data monitoring committee
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOT	End-of-treatment
FPFV	First patient first visit
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FGFR1-3	FGFR1, FGFR2 or FGFR3
GnHR	Gonadotrophin-releasing hormone receptor
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
Hpf	High power field
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LPLV	Last patient last visit
MATE1	Multidrug and toxin extrusion protein 1
MEDRA	Medical Dictionary for Regulatory Activities

mmHg	Millimetres of mercury
MRI	Magnetic resonance imaging
MRT	Mean residence time
ms	Millisecond
MSRA	Methicillin-Resistant Staphylococcus Aureus
mITT	Modified intent-to-treat
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OCT2	Organic cation transporter 2
ORR	Objective response rate
OS	Overall Survival
PD	Progressive disease
PDX	Patient-derived xenograft
PDy	Pharmacodynamics
PFS	Progression-free survival
P-gp	P-glycoprotein
[redacted]	[redacted]
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
[redacted]	[redacted]
PS	Performance status
PTF	Peak-to-Trough fluctuation
QD	Once daily
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using Fridericia 's formula
RD	Recommended dose
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Stable disease
SOC	Standard of care
$t_{½}$	Apparent terminal half-life
TACC	Transforming acidic coiled-coil
TEAE	Treatment emergent adverse event
t_{max}	Time to maximum concentration
ULN	Upper normal limit
V_z/F	Apparent volume of distribution during the terminal phase
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WMA	World Medical Association
λ_z	Apparent elimination rate constant during the terminal phase

DEFINITION

Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. According to the above definition, the Debiopharm International SA active substance being tested during the study is considered as IMP.

RATIONALE FOR PROTOCOL AMENDMENT Nº 2

The results of an initial statistical review of pooled data showed that the antitumor activity of Debio 1347 is 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 DMC on June 10th, 2020.

Despite the lower than expected efficacy, there are ongoing subjects who are deriving benefit from the treatment, as per the opinion of their treating physician. For ethical reasons, the Sponsor intends to continue supplying study medication to these subjects until disease progression, unacceptable toxicity, subject withdrawal, or loss to follow up.

For all subjects who will remain on treatment with Debio 1347 after the implementation of Protocol Amendment Nº 2, the assessments and procedures defined in the study protocol will no longer be in force and will be replaced by standard institutional care practice. Subjects must be followed regularly (at least every 2 months) to assess the potential occurrence of safety events and conduct safety laboratory analyses, as described in Table 8.1b. Only safety data will be collected in the electronic case report form (eCRF).

1. INTRODUCTION

The fibroblast growth factor receptor (FGFR) cascade plays crucial roles in tumor cell proliferation, angiogenesis, migration and survival. Activation of FGFRs as a result of amplification, mutation or translocation of FGFR genes, overexpression of FGFR proteins and amplification or overexpression of fibroblast growth factor (FGF) ligands is known to cause cancer.[1,2]

With the progress of tumor genomic sequencing, numerous recent communications have further documented FGFR oncogenic chromosomal translocations in solid tumors as important oncogenic drivers that fuse in-frame the tyrosine kinase domains of FGFR receptors to numerous partner genes. Most of them contain domains that facilitate dimerization as a proposed mechanism for the oncogenicity of FGFR fusions. FGFR1 and FGFR3 fused to the transforming acidic coiled-coil (TACC) coding domains of TACC1 and TACC3 have thus been described in glioblastoma multiforme (GBM).[3] FGFR3-TACC3 fusions as well as FGFR3-BAIAP2L1 fusion have also been identified in bladder and lung cancers and it has been demonstrated that they are extremely sensitive to FGFR-selective inhibitors[4,5] (see Table 1-1 below). Other fusion partners for FGFR1, FGFR2 and FGFR3 (FGFR1-3) have been described in a wide spectrum of solid tumors including lung adenocarcinoma[6], lung squamous cell carcinoma, breast cancer, intrahepatic cholangiocarcinoma[7], thyroid cancer, prostate cancer, oral cancer.[8,9] Furthermore, reductions in tumor burden of FGFR2 fusion positive cholangiocarcinoma subjects have been observed when treated either with FGFR selective inhibitors or multikinase inhibitors that target FGFR1.[10,11] Finally other mechanisms of oncogenicity of FGFR fusions such as promoter switching or loss of microRNA regulation have been recently described. Preclinical testing in cancer cell lines suggest that FGFR gene fusions can be an important mechanism of tumor progression that may be effectively targeted with FGFR inhibitors.[8,9]

Table 1-1 Frequency of FGFR fusions in solid cancers

Cancer types with reported fusions	Range of fusion frequency in the literature	Fusion frequencies reported in a real life harmonized database (covering 10 336 subjects)[12]
Ampullary carcinoma	4.00%	4.00%
Breast cancer	0.08%-0.49% [8,12-15]	0.08 %
Cervical Cancer	3.85% [16]	N/A
iCCA [7,12,14,17,18]	3.5%-13.64%[i]	7.44%
Colorectal cancer IBD-associated CRC	0.10%-0.67% [7,19] 2.13%[20]	0.10 % N/A
Endometrial cancer	0.47%-1.20% [12,14]	0.47%
Gallbladder cancer	1.17%	N/A
Gastric adenocarcinoma	0.35%-1% [13-15,21]	N/A
Germ cell tumor	0.37% [12]	0.37%
Glioblastoma	1.23%-8.3% [3,8,13,15,22-26]	N/A
Glioma	0.65% - 1.95% [12-15,24,26]	1.95%
Head & neck squamous cell carcinoma	0.49%-1.42% [6,8,12,13,15,26-30]	0.56%
Hepatocellular carcinoma	1.04%	N/A
Lung adenocarcinoma	0.59%-1.95%[6,27]	N/A
Lung squamous cell carcinoma	0.26%-6.17% [8,12,13,15,23,26,28,29,31,32]	N/A
Ovarian cancer	0.25% [13]	N/A
Pancreatic carcinoma	0.20%-1% [12,14]	0.20%

[i] One publication reports a frequency of FGFR fusion in up to 44.86% in iCCA cases (Sia et al., 2015). This represents the highest percentage reported in the literature and its reliability is discussed within the medical community. This result comes from a single institution and relatively small cohort. As a population or technical bias cannot be excluded and the majority of other literature have a more harmonized reported percentage, the applicant has not considered it for the incidence calculation.

Cancer types with reported fusions	Range of fusion frequency in the literature	Fusion frequencies reported in a real life harmonized database (covering 10 336 subjects)[12]
Prostate adenocarcinoma [8,12,13,15]	0.16%-3.23%	0.16%
Renal cell carcinoma	0.51%-1.04% [7,14,15]	N/A
Soft tissue sarcoma (STS) Phosphaturic mesenchymal tumors	0.23% [12] 60%[33]	0.23%
Thyroid carcinoma	0.42% [8]	N/A
Unknown primary cancer	1.25% [12]	0.25%
Urothelial carcinoma (including bladder cancer)	1.48%-6.25% [4,8,12-15,23,26,34-36]	1.48%

2. RATIONALE

Debio 1347 is a newly identified low-molecular-weight inhibitor that has a benzimidazole skeleton and is selective for FGFR1-3 (IC_{50} of 9.3, 7.6 and 22 nmol/L, respectively). Debio 1347 has demonstrated a selective anti-proliferative effect on cancer cell lines that have FGFR genetic alterations or overexpress FGFR, but did not inhibit proliferation of cancer cell lines that do not have FGFR genetic alterations or overexpress FGFR.[37]

Debio 1347 has demonstrated anti-tumor activity *in vivo* in bladder cancer models harboring FGFR3-TACC3 or FGFR3-BAIAP2L1 fusions.[37]

The selective FGFR inhibitor Debio 1347 has in addition been shown to exert anti-proliferative activities *in vitro* and antitumor activity *in vivo* in xenograft models harboring two FGFR2 fusions first identified in intra-hepatic cholangiocarcinoma subject samples.[38]

Debio 1347 was able to induce tumor regressions in subject-derived xenograft models (PDX) harboring FGFR fusions in brain, breast, gastric and liver cancer.

The dose-escalation portion of the first-in-human Phase I study of Debio 1347 has recently been completed.[39] Debio 1347 had a manageable safety profile. Encouraging antitumor activity was seen in several tumor types, mainly in subjects with FGFR2 or 3 gene alterations, including fusion events. In particular, 3/10 subjects with FGFR fusions treated at doses ≥ 60 mg daily had a partial response (PR) and 4/10 subjects had a target regression < 30%. Disease control rate (DCR) for subjects with FGFR fusions was 80%.

The above led to the evaluation of Debio 1347 in FGFR fusion-positive tumors.

3. PHARMACEUTICAL AND BACKGROUND INFORMATION

3.1. Debio 1347 Chemical Structure, Formula, and Molecular Weight

Structural formula:

Chemical name: [redacted]

Molecular weight: 490.47l

Molecular formula: $C_{20}H_{16}N_6O•C_4H_6O_5$

3.2. International Non-proprietary Name, Brand Name, and Code Name

INN (International Non-proprietary Name)	Not applicable
Brand name:	Not applicable
Company code name:	Debio 1347 malate (malate salt)
	Debio 1347 (free base)
Former code name:	CH5183284

3.3. Brief Summary of Non-clinical and Clinical Data

3.3.1. Non-clinical data

FGFRs are expressed on many different cell types and regulate key cell behaviours such as proliferation, differentiation and survival, and render FGF signalling susceptible to subversion by cancer cells.[40] Activation of FGFRs as a result of amplification/mutation/translocation of FGFR genes, over-expression of FGFR proteins or overproduction of ligands has been shown to be oncogenic in many cancer cell types. Alterations in FGF/FGFR signalling ultimately lead to up regulation of the MAPK and PI3K-Akt signalling pathways. Dysregulation of FGFR-dependent signalling can contribute to tumour growth and angiogenesis through a variety of mechanisms.[41] FGFR alterations are thus promising therapeutic targets in cancer.

The orally-active small molecule Debio 1347 is an ATP competitive and highly selective inhibitor of FGFR1-3 at the low nanomolar level in cell-free systems (IC_{50}: 7.6 – 22 nM). Preclinical studies have shown that Debio 1347 is effective in multiple tumour models of different origins with FGFR alterations.

Pharmacology – in vitro

Debio 1347 is an ATP competitive inhibitor of FGFR1-3 tyrosine kinases at the low nanomolar level (IC_{50}: 7.6–22 nM) with less potent inhibitory activity on FGFR4 (290 nM) in cell-free systems. The compound is highly selective and does not act on VEGF receptor kinase KDR as demonstrated in vascular endothelial cells.

Debio 1347 has predominant activity against FGFR1-3 and has been shown in vitro to display anti-proliferative activity in tumor cell lines with either amplification, mutation or fusion/rearrangement of the FGFR1-3 genes or overexpression of FGFR(s).

No anti-proliferative activity was observed for cell lines without FGFR genetic alterations or high expression. More specifically, out of 327 cell lines tested, 31 harboured a FGFR gene alteration, of which 20 (64.5%) were classified as sensitive to Debio 1347 (with an IC_{50} below or equal to 1µM). Looking more closely at the different types of alterations, 100% of cell lines (5/5) that harboured FGFR fusions were sensitive to the inhibitor whereas, in the presence of mutation or amplification, only 50% (5/10) and 62.5% (10/16) of the tested cell lines were found to be sensitive to Debio 1347. This suggests that cancer cell lines harbouring FGFR fusions are the most sensitive to FGFR inhibition.[37]

Pharmacology – in vivo

Debio 1347 potently inhibits cell growth in a dose-dependent manner in multiple tumour models of various origins with FGFR genetic alterations and in particular in models harbouring FGFR fusions. For example, Debio 1347 showed potent anti-tumoral activity in patient-derived xenograft (PDX) models of gastric cancer harbouring FGFR2-WDR11 fusion and lung cancer with FGFR2-MCU fusion. Debio 1347

administration induced tumor regressions in PDX models of liver cancer harbouring FGFR2-CCDC6 fusion, in a brain cancer model harbouring FGFR3-TACC3 fusion and a breast PDX model harbouring FGFR2-GAB2 fusion at non-toxic doses.

Overall, the results suggest that subjects with FGFR1-3 fusions/rearrangements could benefit from targeted FGFR1-3 inhibitors such as Debio 1347.

Please refer to the Investigator's Drug Brochure for more information.

Toxicology and Safety Pharmacology

The toxicology profile of Debio 1347 was assessed after single and repeated oral administration in Wistar rats and Cynomolgus monkeys for up to 4 weeks and in a battery of safety pharmacology tests in vitro and in vivo.

In the 4-week GLP-compliant repeated-dose toxicity study in rats (0, 3, 10, 30 mg/kg/day), no deaths occurred at any Debio 1347 dose up to the highest dose of 30 mg/kg/day. At 30 mg/kg/day, thoracic deformity was seen in the general condition observations, and changes in cartilage and bone including the sternum were seen in the histopathological examinations. Mineralisation in multiple organs, changes in epithelial tissues and changes in parameters of blood and urine related to renal function were also observed. The above-mentioned histopathological changes were not seen at 10 mg/kg/day or less, mainly changes in parameters of blood and urine that suggested effects on bone were observed. At the lowest dose of 3 mg/kg/day, high blood TRACP-5b (tartrate-resistant acid phosphatase 5b, a bone resorption marker) was seen, so the no observed adverse effect level was judged to be less than 3 mg/kg/day. The no observed adverse effect level (NOAEL) was considered to be lower than 3 mg/kg/day.

In the 4-week GLP-compliant repeated-dose toxicity study in monkeys (0, 0.4, 1.3, and 4 mg/kg/day), no deaths occurred at any Debio 1347 dose up to the highest dose of 4 mg/kg/day. At 4 mg/kg/day, very slight histopathological changes in bone and cartilage and related changes in parameters of blood and urine were seen, and in one female, very slight histopathological changes in kidneys were observed. At the middle dose of 1.3 mg/kg/day, only high urinary excretion of inorganic phosphorus in females was seen. No effects were observed at the lowest dose of 0.4 mg/kg/day, so that was judged to be the no observed adverse effect level in this study. On the basis of these results, the HNSTD (highest non-severely toxic dose for monkeys) was set at 4 mg/kg/day (NOAEL: 0.4 mg/kg/day).

The principal target organs of Debio 1347 toxicity in rats and monkeys were bone/cartilage, epithelial tissues and the kidneys. In addition, effects on lymphohematopoietic tissues, liver and the gastrointestinal tract were observed. Mineralisation in multiple organs was also seen, with a broader range of organs and tissues affected in rats than in monkeys. On the other hand, periosteal changes occurred only in monkeys but not in rats. Except for thoracic deformity and mineralisation in multiple organs in rats, the changes seen in rats and monkeys in the 4-week repeated-dose toxicity studies either reversed or tended to reverse over the 4-week recovery period.

Debio 1347 was not considered to be genotoxic on the basis of bacterial reverse mutation, chromosomal aberration in vitro and micronucleus and Comet assays in vivo in rats.

Debio 1347 may have an in vivo phototoxic risk based on 1) an in vitro phototoxicity test using a fibroblast cell line (absorbance wavelengths of 200 nm to 400 nm) and 2) a whole-body autoradiography in rats suggesting a slower elimination rate of Debio 1347 from skin compared with blood. Subjects should avoid excessive exposure to sun/UV light while undergoing treatment with Debio 1347.

Although dedicated reproductive and developmental toxicity studies of Debio 1347 have not been conducted so far, some changes such as thinning of vaginal mucosal epithelium and atrophic changes in testes, epididymides, prostate gland, seminal vesicles and uterus were observed at lethal dose in preliminary dose-repeated toxicity in rats. From the above findings and those on bone and cartilage, it is inferred that Debio 1347 may affect reproduction and development.

Results of safety pharmacology studies performed with Debio 1347 showed that the compound had no effects on the central nervous or respiratory systems in rats at doses up to 100 mg/kg. Although a significant

hERG inhibition (IC_{50}, 677 ng/mL) was seen in vitro, there were no effects on blood pressure (BP), heart rate, electrocardiogram (ECG) or body temperature in monkeys at doses up to 10 mg/kg. According to calculations based on free Debio 1347 (plasma protein binding around 99%), the plasma concentrations required to induce a given level of inhibition would be about 100 times greater than the concentration inducing the same level of inhibition in vitro. The ratio of 50% inhibitory concentration (IC_{50}) for the hERG assay to the free plasma concentration of drug required for clinical efficacy (i.e., 25 ng/mL of unbound C_{max}, based on 99.0% protein binding and mean C_{max} of 2486 ng/mL at steady-state of the RD of 80 mg/day in study Debio 1347-101 – dose-escalation phase) was used as an index of proarrhythmic potential; the ratio was 27, giving a significant apparent safety margin.

No carcinogenicity studies or local tolerance studies have been conducted to date.

Please refer to the Investigator's Brochure for more information.

Rationale for dose selection

The dose of 80 mg/day to be administered in this study is based on the RD determined in the previous study Debio 1347-101.

3.3.2. Clinical data

The dose-escalation part of the first-in-human, multicenter, open-label study Phase I study of Debio 1347 (study Debio 1347-101) was recently completed.[39]A total of 58 subjects with genomically activated advanced solid tumours were included and treated with Debio 1347 at doses from 10 to 150 mg/day. All were assessable for safety. Of these, 57 were evaluable for efficacy. Median treatment duration was 7.3 weeks (range 0.1 – 72).

All 58 treated subjects experienced ≥ 1 treatment emergent adverse event (TEAE) of which the highest severity was Grade 1 in 4 (6.9%), Grade 2 in 17 (29.3%), Grade 3 in 28 (48.3%), Grade 4 in 2 (3.4%) and Grade 5 in 7 (12.1%) subjects. The most common TEAEs with an incidence > 25% were hyperphosphatemia, diarrhea, nausea, fatigue, constipation, decreased appetite and dry mouth. Nail changes (includes nail bed disorder, nail discoloration, nail dystrophy, onychalgia, onychoclasis and onychomadesis) were reported in 11 subjects. The most severe TEAEs were Grade 5 disease progression in 4 (6.9%) subjects and respiratory failure, sepsis and a new neoplasm (endometrial cancer) each in one subject (1.7%). They were not drug-related. Hyperphosphatemia, anemia, hyponatremia and dyspnea were most often severe (i.e., Grade > 2). A total of 54 (93%) subjects experienced TEAEs considered as related to Debio 1347.

Twenty subjects experienced 39 serious adverse events (SAEs), most commonly dyspnea, but only two SAEs were deemed possibly study drug related and thus dose limiting toxicities (DLTs), i.e., Grade 3 hyperamylasemia (80 mg) and Grade 3 stomatitis (110 mg). DLTs occurred in 3 other subjects, i.e., Grade 2 dry mouth and eyes (60 mg) in one subject; Grade 3 asymptomatic hypercalcemia (80 mg); Grade 3 bilirubin increase and hyperphosphatemia (110 mg) in one subject. The subject with hyperamylasemia died from disease progression. The remaining 4 subjects recovered after Debio 1347 interruption and/or dose modification. As there were only ≤ 2 DLTs at the same dose level, the MTD (maximum tolerated dose) was not formally reached. No further dose-escalation was carried out.

Decreased left ventricular ejection fraction (LVEF) was reported in 1 subject (Grade 2) and 3 subjects experienced non-clinically significant Grade 1 (n = 2) and Grade 2 (n = 1) ECG QTc prolongation.

Overall, 21 subjects died from disease progression; no death was considered drug-related.

Although a cohort of 3 subjects completed the first treatment cycle at 150 mg once daily without experiencing any DLT, the safety data showed an increased incidence of adverse events (AEs) and Grade 3 AEs during dose-escalation from 80 to 110 to 150 mg. The 80 mg dose once daily was therefore selected as the recommended Phase 2 dose and hence the dose level to be administered in the expansion part of the study. The expansion part is still ongoing.

No trend towards QTc prolongation was evident from the local ECG measurements collected during the study. An additional exposure-response analysis based on ECG central reading was not fully conclusive regarding the QTcF prolonging potential of Debio 1347, but indicate that the potential increase (predicted upper bound of the 90% CI for ΔQTcF was 11.44 and 12.55 milliseconds at the recommended dose of 80 and the highest dose of 150 mg, respectively) would remain below the 20 milliseconds threshold usually considered for oncology products. Furthermore, there were no relevant changes for the other ECG intervals of interest (QRS, RR, PR) after Debio 1347 and no relevant changes were evident from the categorical analysis or from the analysis of morphological abnormalities.

A total of 57 subjects were evaluable for tumor response. One subject had no measurable disease. Best overall response was progressive disease (PD) in 35 subjects and stable disease (SD) in 16 subjects, of whom 10 showed reduced target lesion size at least once post-dose; the remaining 6 subjects had PR (2 unconfirmed). Of these six PRs, two had urothelial carcinoma (80, 150 mg), the others endometrial (30 mg), cervical (80 mg), inflammatory bowel disease-associated colorectal cancer or cholangiocarcinoma (both 110 mg). For the latter the independent centralized radiological review changed response from partial to confirmed complete response (CR) and of the 2 unconfirmed PRs one became confirmed. Among 10 subjects with confirmed FGFR fusions treated at doses ≥ 60 mg/day, 3 achieved PRs and 5 disease stabilization. This represents a DCR in this subpopulation of 80% (vs 38.6% overall). The median treatment duration in subjects with disease control was 34 weeks (range: 24-47).

Upon oral dosing in fasted conditions, Debio 1347 was rapidly absorbed with a median t_{max} of 3 hours, followed by a mono-exponential decrease of plasma levels with a mean half-life of 11.5 hours. Mean apparent oral clearance was 7 L/h and mean volume of distribution 110 L. Inter-individual pharmacokinetic (PK) variability was 32 to 48%. The increase of Debio 1347 plasma exposure was approximately dose-proportional over doses from 10 to 150 mg. In line with the half-life and 24-hour dosing intervals, a limited accumulation was observed at the end of the first treatment cycle, with on average 1.9 and 1.7 times higher $AUC\tau$ and C_{max} after 28 days of repeated once daily dosing, respectively. Trough levels indicated that steady-state was achieved in the majority of subjects during the first week of treatment. Overall, Debio 1347 PK is linear and supports a once daily dosing regimen.

Please refer to the Investigator's Brochure for more information.

3.3.3. Risk-benefit Assessment

In the non-clinical setting, Debio 1347 exhibits high anti-tumour activity both in vitro and in vivo in cancers with amplification, mutation or translocation/fusion of the FGFR1, 2 or 3 genes, and cancers with overexpression of FGFR(s). This compound is regarded as an innovative therapeutic opportunity for cancer patients with genetic alterations in the FGFR1-3 genes or overexpression of the FGFR1-3 proteins.

In non-clinical safety studies of Debio 1347 in rats and monkeys, the principal target organs of toxicity were bone/cartilage, epithelial tissues and the kidneys. In addition, effects on lymphohaematopoietic tissues, liver and the gastrointestinal tract were observed. Mineralisation in multiple organs was also seen (such as trachea, stomach, kidneys, eyes in rats), with a broader range of organs and tissues affected in rats than in monkeys. On the other hand, periosteal changes occurred only in monkeys but not in rats. Except for thoracic deformity and mineralisation in multiple organs in rats, the changes seen in rats and monkeys in the 4-week repeated-dose toxicity studies either reversed or tended to reverse over the 4 week recovery period.

As a result, soft-tissue mineralisation, bone/cartilage effects, lymphohaematopoietic abnormalities, gastrointestinal and hepatic disorders, and ophthalmological disorders (mainly corneal mineralisation) are under close monitoring in the clinical setting. Subjects with phosphate/calcium homeostasis impairment are contraindicated. In addition, subjects with osteoporosis should be closely monitored. Investigators should reassess the risk-benefit ratio for each of their subjects.

Debio 1347 may have an in vivo phototoxic risk based on an in vitro phototoxicity test using a fibroblast cell line, where the compound was suggested as a phototoxic substance; and a whole-body autoradiography in rats after single oral dose of 1 mg/kg of [^{14}C] Debio 1347 suggesting a slower elimination rate of Debio

1347 from skin compared with blood. On the basis on these findings, subjects should avoid excessive exposure to sun/UV light.

Although reproductive and developmental toxicity studies of Debio 1347 have not been conducted, some changes in the reproductive organs, such as thinning of vaginal mucosal epithelium and atrophic changes in testes, epididymides, the prostate gland, seminal vesicles and the uterus were observed at the lethal dose in preliminary dose-repeated toxicity studies in rats. From these findings and those reported above on bone and cartilage, it is inferred that Debio 1347 may affect reproduction and development; pregnancy/breastfeeding are therefore strictly contraindicated.

In safety pharmacology studies, no effects on the central nervous system or respiratory system were seen in rats at Debio 1347 doses up to 100 mg/kg. Debio 1347 was a potent hERG inhibitor in vitro, but the compound did not modify blood pressure, heart rate, and ECG or body temperature at doses up to 10 mg/kg in the monkey telemetry study. Although Debio 1347 potential for affecting cardiac function is considered to be low based on the study in monkeys, this potential risk is under close monitoring in the ongoing Phase I trial.

Based on current knowledge, Debio 1347 is deemed to have a limited risk of being victim of PK interaction from other drugs. In contrast, as per in vitro results available so far, Debio 1347 is considered at possible risk for perpetrating DDIs towards sensitive substrates of CYP1A2, CYP3A, P-gp, BCRP, MATE1 and OCT2 through inhibition and/or induction of drug metabolism or transport. In addition, BSEP may be inhibited as well.

The clinical impact of these in vitro observations is not known. Subjects who are taking concurrent drugs that are known substrates of either CYP3A, CYP1A2, P-gp, BCRP, MATE1 or OCT2 should be carefully monitored. In addition, potential changes in bile salts plasma concentration should be monitored during treatment with Debio 1347.

Carcinogenicity studies or local tolerance studies have not been conducted to date.

Concerning efficacy, clinical activity of Debio 1347 started at the dose of 30 mg. In the dose escalation portion of the Phase I trial, a total of 57 subjects were evaluable for tumor response. One subject had no measurable disease. Best overall response was PD in 35 subjects and SD in 16 subjects, of whom 10 showed reduced target lesion size at least once post-dose; the remaining 6 subjects had PR (2 unconfirmed). Of these six PRs, two had urothelial carcinoma (80, 150 mg), the others endometrial (30 mg), cervical (80 mg), inflammatory bowel disease-associated colorectal cancer or cholangiocarcinoma (both 110 mg). For the latter the independent centralized radiological review changed response from partial to confirmed CR and of the 2 unconfirmed PRs one became confirmed. Among 10 subjects with confirmed FGFR fusions treated at doses $\geq$ 60 mg/day, 3 achieved PRs and 5 disease stabilization. This represents a DCR in this subpopulation of 80% (vs 38.6% overall). The median treatment duration in subjects with disease control was 34 weeks (range: 24-47).

The safety population comprised 58 subjects of which 20 reported 39 SAEs. Two of these were considered as having a reasonable causal relationship with Debio 1347. One subject developed NCI-CTCAE Grade 3 hyperamylasaemia 23 days after intake of the first dose of Debio 1347. The Investigator considered causality as possibly related to the study drug, even though the subject presented with dilatation of the main pancreatic duct, suggesting previously unknown chronic pancreatitis. Moreover, concomitant medications (pravastatin, captopril, ranitidine and codein) could have contributed to the occurrence of this event. One subject experienced NCI-CTCAE Grade 3 stomatitis, which decreased to Grade 1 after holding the drug for 8 days.

The most common AEs (> 25%) irrespective of relationship with the study drug were hyperphosphatemia, diarrhea, nausea, fatigue, constipation, decreased appetite and dry mouth, all of which were generally mild and manageable. Nail changes (includes nail bed disorder, nail discoloration, nail dystrophy, onychalgia, onychoclasis and onychomadesis) were reported in 11 subjects.

Decreased LVEF was reported in 1 subject (Grade 2) and 3 subjects experienced non-clinically significant Grade 1 (n = 2) and Grade 2 (n = 1) ECG QTc prolongation. Data are limited and ECG monitoring is warranted for all subjects included in clinical studies of Debio 1347.

No trend towards QTc prolongation was evident from the local ECG measurements collected during the study. An additional exposure-response analysis based on ECG central reading was not fully conclusive regarding the QTcF prolonging potential of Debio 1347, but indicate that the potential increase (predicted upper bound of the 90% CI for ΔQTcF was 11.44 and 12.55 milliseconds at the recommended dose of 80 and the highest dose of 150 mg, respectively) would remain below the 20 milliseconds threshold usually considered for oncology products. Furthermore, there were no relevant changes for the other ECG intervals of interest (QRS, RR, PR) after Debio 1347 and no relevant changes were evident from the categorical analysis or from the analysis of morphological abnormalities.

To mitigate the inherent risks in the current clinical study of Debio 1347, subjects are closely monitored while they are receiving treatment.

Debio 1347 seems to be generally well tolerated and the observed toxicity profile to date has been consistent with the expected effect of a selective and potent inhibitor of the FGFR pathway, the benefit/risk profile is assessed as positive. Further clinical research with Debio 1347 is therefore warranted.

4. OBJECTIVES

4.1. Objectives

4.1.1. Primary objective

To assess the efficacy of Debio 1347 in terms of objective response rate (ORR) in subjects with solid tumors harboring FGFR1-3 gene fusion/rearrangement.

4.1.2. Secondary objectives

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

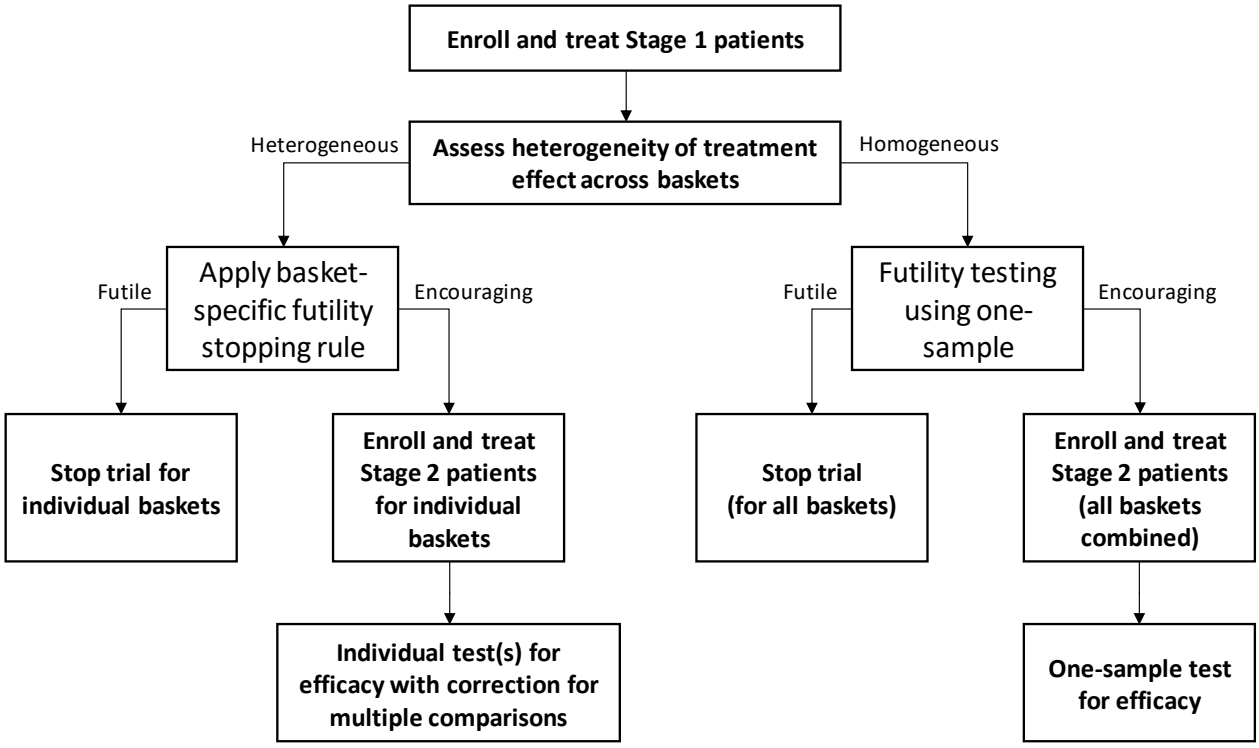
[redacted]

5. STUDY DESIGN AND TREATMENT

5.1. Study Design

This is a is a multicentre, basket[42], two stage, adaptive single arm Phase II study to examine the efficacy of Debio 1347 administered at the recommended Phase II 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 Cohorts 1-2, 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 graphical algorithm below and Section 11). Assuming a drop out rate of 10%, up to 125 subjects will be enrolled into the study.



Subjects will be treated with Debio 1347 daily in 28-day cycles until the occurrence of disease progression (clinical or radiologic) or unacceptable toxicity (other treatment discontinuation criteria are described in Section 8.4.1). 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.

5.2. Study Treatment

Subjects will receive Debio 1347 tablets at the dose of 80 mg once daily from Day 1 to Day 28 in 28-day cycles until occurrence of any of the criteria described in Section 8.4.1.

Debio 1347 method of administration is described in Section 7.6.

5.3. Dose Modifications

5.3.1. Debio 1347 dose adjustment

Individual dose adjustment of Debio 1347 may be considered and applied as per Table 5-1 below if required. Non-treatment related or unexpected toxicities may also require treatment interruption at the discretion of the Investigator and Medical Monitor. For guidance on toxicity management, please refer to appendices E, F, and G.

Table 5-1 Debio 1347 dose adjustment

ADVERSE EVENT	GRADE	ACTION
Febrile neutropenia, Neutropenia with infection	4	Permanent discontinuation
	3	Temporary discontinuation until recovery to ≤ Grade 1
Neutropenia	3, 4	Temporary discontinuation until recovery to ≤ Grade 2
Thrombocytopenia	4	Temporary discontinuation until recovery to ≤ Grade 1
	3	If a platelet transfusion is required, temporary discontinuation until recovery to ≤ Grade 1
Diarrhea, constipation, nausea, vomiting, alopecia or skin toxicity	3, 4	Temporary discontinuation until recovery to ≤ Grade 1, but Grade 2 diarrhea manageable with drugs can restart the treatment at 60 mg QD
Hypertension	4	Permanent discontinuation
	3	If uncontrolled, temporary discontinuation until recovery to ≤ Grade 2
Hepatotoxicity (e.g., AST, ALT, ALP increased)	4	Permanent discontinuation
	3	Temporary discontinuation until recovery to ≤ Grade 2
Other non-hematological toxicity (except for alopecia and clinically insignificant electrolyte abnormalities)	4	Permanent discontinuation
	3	Temporary discontinuation until recovery to ≤ Grade 1 or baseline
Hyperphosphatemia		Please refer to treatment guidelines in Appendix E
Recovery from the above AEs		Permanent discontinuation if failure to recover within 21 days, otherwise retreatment at 60 mg QD
Dermatologic toxicities		Please refer to treatment guidelines in Appendix F
Hypercalcemia		Please refer to treatment guidelines in Appendix G

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; QD, once daily

In the event a subject requires temporary treatment discontinuation, the Investigator may choose to increase the frequency of the assessments until resolution.

Subjects will be permanently discontinued if a second reduction is necessary. Reduced doses may not be re-escalated. Nevertheless, if according to the Investigator a further increase of the dose to 80 mg daily is expected to improve the clinical benefit of a subject, this increase may be considered after discussion between the Investigator and the Medical Monitor of the study.

5.3.2. Guideline for significant QTcF prolongation

Significant QT interval corrected for heart rate using Fridericia 's formula (QTcF) prolongation is defined as an interval > 500 ms or an interval which increases by 60 milliseconds (ms) over baseline.

A. If the prolongation is confirmed on a repeated ECG by **either** criterion (i.e., QTc interval > 500 ms **or** > 60 ms increase from baseline) the following actions will be taken:

   - The subject will be monitored, treated appropriately and closely followed (ECGs at least three times per week) until the QTc interval returns to within 30 ms of baseline.
   - The Medical Monitor will be consulted prior to administering further doses or re-challenging.

   If an ECG shows significant QTc prolongation the subject should be referred to a cardiologist.

B. If the prolongation is confirmed on a repeated ECG by **both** criteria (i.e., QTc interval > 500 ms **and** > 60 ms increase from baseline) treatment with Debio 1347 should be discontinued and the following actions taken:

   - The subject will be monitored, treated appropriately and closely followed (ECGs at least three times per week) until the QTc interval return to within 30 ms of baseline.

   If an ECG shows significant QTc prolongation the subject should be referred to a cardiologist.

6. STUDY POPULATION

Subjects with locally advanced (unresectable) or metastatic tumors with FGFR1-3 gene fusion/rearrangement who require systemic therapy and who have radiologic and/or clinical progression following at least one prior standard treatment or who have no satisfactory alternative treatment options.

6.1. Inclusion Criteria

Potential participants who fulfil the criteria below will be included:

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.
6. 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) (see Appendix A) performance status (PS) of 0 to 1.
9. Screening laboratory values as follows:
    a. Absolute neutrophil count (ANC) ≥ 1,000/mm^3 [1.0 x 10^9/L].
    b. Platelet count ≥ 75,000/mm^3 [75 x 10^9/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 see Section 7.7.1.

    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.

    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.

12. Life expectancy ≥ 3 months.

6.2. Exclusion Criteria

Any of the following would render a subject ineligible for inclusion:

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.

6.3. Subject Replacement

No subjects will be replaced.

7. CLINICAL SUPPLIES

7.1. Investigational Medicinal Product – Debio 1347

Composition:	Debio 1347 20 mg tablets containing the following excipients: lactose hydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate.
Dosage form:	White coated tablets.
Presentation:	28 tablets in [redacted] blisters.
Expiry date:	Shelf life will be updated when new stability data are available.
Storage:	Mentioned on labels.

A certificate of analysis (CoA) will be provided with the product.

7.2. Packaging and Storage of Investigational Medicinal Product

7.2.1. Packaging

Debio 1347 tablets packed in [redacted] blisters will be delivered to study site pharmacies by the Sponsor. Each blister will contain 28 tablets of Debio 1347 20 mg.

The site Pharmacist will deliver to the subjects the number of Debio 1347 blisters required.

7.2.2. Labelling

Labelling will be open and will comply with the health authority regulations of each participating country.

7.2.3. Storage

Storage conditions will be specified on the labels.

7.3. Dispensing and Accountability of Investigational Product

The IMP and CoA will be provided to the Investigator(s) by and under the responsibility of the Sponsor, who will also ensure release of the IMP as per current GMP (Good Manufacturing Practice) guidelines. Any documentation required by local health authorities for import of the IMP will be appropriately submitted.

The Investigator/Pharmacist at each study site will inventory and acknowledge receipt of all shipments of IMP. The IMP accompanied by analytical reports when appropriate, must be kept in a locked area with access restricted to designated study personnel and must be stored in accordance with the manufacturer's instructions.

The Investigator/Pharmacist at each study site will keep accurate records of the IMP (and other study-related drugs) dispensed. These records will specify dates and amounts dispensed, to and by whom (drug dispensing list) and report any IMP accidentally or deliberately destroyed.

At timely intervals and study closure, the IMP will be reconciled by the Sponsor’s monitor/representative according to the Sponsor's standard operating procedure (SOP) unless otherwise agreed. Unused IMP will be counted and destroyed only after formal written agreement has been received from the Sponsor. Any discrepancies between the IMP returned and the expected balance must be justified.

Unused IMP must not be used for any purpose other than the present study.

7.4. Subject Numbering

7.4.1. Pre-screening number in the case of central FGFR assessment

Only subjects who require a central assessment of FGFR status will be manually assigned a unique pre-screening number by the site. The pre-screening number consists of a unique 7-digit identifier (###9###). The first 3 digits represent the number of the study centre, the hardcoded "9" refers to the pre-screening process and digits 5-6-7 identify the pre-screening order of the subject at the centre (starting at 001). *Pre-screening* # 1069001, for example, identifies the first subject (001) pre-screened at study centre 106. The second subject pre-screened at the same study centre will be given *Pre-screening* # 1069002, etc.

The above subjects will not be recorded in the electronic case report form (eCRF) if their eligibility is not confirmed by the pre-screening FGFR fusion/rearrangement assessment (see Section 8.2.1.1). Conversely, eligible subjects will proceed with the scheduled screening procedures and will be assigned a screening number as described below. The pre-screening number will then be entered in a specific field of the eCRF via the internet-based application. The pre-screening number described above is different and separate from the screening number described in the next section.

Each site must keep the pre-screening log to document the subjects who have been pre-screened at their site.

7.4.2. Screening number

At **the first screening visit between Days -28 and -1 prior to study start**, each potential study subject will be identified by a unique *Screening number (*#) which is automatically displayed when the subject is initially recorded in the IWRS (Interactive Web Response System) via the internet-based application, and the subject will be created with the same *Screening* # in the e-CRF by an automated data integration from the IWRS. The *Screening* # allows entry of subject data in the eCRF.

The *Screening* # consists of a unique 6-digit identifier. The first 3 digits represent the number of the study centre and digits 4-5-6 identify the screening order of the subject at the centre (starting at 001). *Screening* # 106001, for example, identifies the first subject (001) screened at study centre 106. The second subject screened at the same study centre will be given *Screening* # 106002, etc.

7.5. Blinding and Unblinding Methods

Not applicable.

7.6. Method of Administration and Compliance

Debio 1347 tablets will be administered orally at the dose of 80 mg once daily from Day 1 to Day 28 in 28-day cycles (see study plan in Section 8.3) until occurrence of any of the criteria described in Section 8.4.1.

Debio 1347 will mostly be self-administered by subjects at home and should be taken at approximately the same time each day as follows:

1. Debio 1347 must be taken early in the morning. Subjects must fast (only water permitted freely) for 4 hours before and 2 hours after intake.
2. If a dose is not administered for reasons other than toxicity, the subject may take the dose later in the day but no later than 6 hours after normal intake time. If the delay exceeds 6 hours, the subject must wait until the next scheduled administration.
3. If the subject vomits after Debio 1347 intake, another dose should not be administered, rather wait until the next scheduled dose.

Subjets will also be instructed by study staff on how to take Debio 1347.

Dose adjustments are permitted as described in Section 5.3.

Subject compliance will be verified by a) means of a diary card or equivalent electroninc tool to be filled out after each dose when taken at home and b) direct visual supervision at dosing by the Investigator or designee when the drug is administered at the study site. Compliance will be checked by the Investigator or designee at each study visit and the number of returned tablets and date will be recorded when applicable.

7.7. Concomitant Therapy

7.7.1. Permitted medications

1. Supportive therapies against pain, nausea, vomiting, constipation and diarrhea are allowed as per the Investigator's decision, as well as granulocyte colony-stimulating factors (G-CSF). Treatment of pain should be administered according to severity and recommended drugs. Study specific guidelines will be provided separately.
2. Gonadotrophin-releasing hormone receptor (GnHR) agonists and antagonists for prostate cancer are permitted (if prostate cancer is the reason for eligibility).
3. Bisphosphonates and denosumab: Concomitant use is allowed.
4. Radiotherapy: Concomitant radiotherapy may only be given for the control of bone pain or as indicated to ≤ 30% of the bone marrow. Irradiated lesions will not be evaluable for response. Radiotherapy should start no sooner than 24 hours after the previous dose of Debio 1347 and study treatment may be resumed with the resolution of any radiation toxicity to ≤ Grade 1.

The following medications and/or treatments are permitted with caution and should be monitored during the study:

1. Contact lenses: In non-clinical studies, Debio 1347 has been found to affect the cornea. Since corneal disorders may occur when contact lenses are worn and use of Debio 1347 may exacerbate these symptoms, caution should be exercised when administering Debio 1347 in a subject wearing contact lenses. The subject should be monitored.
2. Drugs with a known risk of QTc prolongation: Considering the QTc prolongation potential (not yet fully characterized) and the risk of hypokalemia associated with Debio 1347, caution should be exercised when using Debio 1347 with drugs having a known risk of QTc prolongation (see Arizona CERT database at website: http://www.crediblemeds.org). Monitoring of electrolyte levels is strongly recommended.
3. Drugs that are known substrates of either CYP3A, CYP1A2, P-gp, BCRP, MATE1 or OCT2:

   Per in vitro results available so far and Debio 1347 plasma exposure observed in subjects, Debio 1347 is considered at possible risk of perpetrating drug-drug interactions through CYP3A inhibition, CYP3A induction (some transporters such as P-gp might also be co-induced), CYP1A2 repression, or inhibition of several transporters (P-gp, BCRP, MATE1, OCT2). The clinical impact of these in vitro observations is not known and subjects who are taking concurrent drugs that are known substrates of either CYP3A, CYP1A2, P-gp, BCRP, MATE1 or OCT2 should be carefully monitored. A list of such drugs can be consulted in:

   Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007) (http://medicine.iupui.edu/clinpharm/ddis/); and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

   It should be noted that the potential for drug-drug interactions with CYP3A or CYP1A2 substrates (and possibly also with P-gp substrates) is time-dependent; it may increase with time as subjects continue to take Debio 1347 and may persist for some days after Debio 1347 discontinuation.

3. Gastric mucosal protectants (e.g. histamine receptor antagonists and antacids but not proton pump inhibitors which are prohibited - see Section 7.7.3) must be taken at least 2 hours after Debio 1347 intake since they may interfere with its absorption.
4. Hormonal contraceptives should be used with caution. Based on in vitro data, Debio 1347 has the potential to induce and/or inhibit CYP3A4 and, as such, exposure and efficacy of hormonal contraceptives might be altered.

Any other medication necessary for the well-being of the subject (with the exception of those mentioned as prohibited medications, see Section 7.7.3 below) may be given at the Investigator's discretion.

7.7.2. Supportive care

7.7.2.1. Dermatological toxicity - prophylaxis and management

Prophylaxis and treatment of dermatological toxicities are described in Appendix F.

7.7.2.2. Gastrointestinal disorders

For nausea, vomiting, diarrhea or constipation, treatment may include antiemetics, antidiarrheals or laxative bowel regimens consistent with SOC. Since drugs that alter gastric pH may interfere with the absorption of Debio 1347, proton pump inhibitors are prohibited during the study (see Section 7.7.3) and other gastric mucosal protectants (e.g. histamine receptors antagonists, antacids) should be administered at least 2 hours after Debio 1347 administration.

7.7.2.3. Hematological support

The use of red blood cell transfusions will be permitted as clinically indicated during the study.

The use of bone marrow colony stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated. Prophylactic use is prohibited.

7.7.2.4. Hypercalcemia management

Subjects with asymptomatic hypercalcemia do not require immediate treatment if calcium remains < 12 mg/dL (3 mmol/L). However, the subject should be advised to avoid factors that can aggravate hypercalcemia (such as thiazide diuretics, volume depletion, prolonged bed rest or inactivity and a high calcium diet [> 1000 mg/day]).

Adequate hydration (at least 6 glasses of water per day) is recommended to minimise the risk of nephrolithiasis.

Hypercalcemia treatment guidelines are described in Appendix G.

7.7.2.5. Hyperphosphatemia management

Subjects will be treated according to the guidelines available in Appendix E.

All enrolled subjects should receive adequate instructions concerning dietary phosphate restriction. Phosphate is a mineral widely found in most foods. The main natural sources of phosphate are:

- Dairy products (milk, cheese, ice-cream, yogurt)
- Meat
- Dried beans
- Peas
- Nuts and peanut butter
- Wholegrains
- Cola

7.7.2.6. Infections

1. CR-BSI (Catheter-Related Bloodstream Infection) should be managed according current Clinical Practice Guidelines.[43]
2. Febrile neutropenia: Antibacterial and antifungal prophylaxis for fever and treatment of neutropenia should be managed according to current clinical practice guidelines.[44,45]
3. MSRA (Methicillin-Resistant Staphylococcus Aureus) infection should be managed according to current clinical practice guidelines.[46]

7.7.3. Prohibited medications

1. Other antineoplastic agents are prohibited except GnHR agonists and GnHR antagonists for prostate cancer.
2. Other investigational agents are not to be used within 2 weeks (3 weeks for immune checkpoint inhibitors) of initial dosing or while receiving Debio 1347.
3. Concurrent radiation treatment, except for palliation or symptom relief. If palliative radiation is indicated for bone metastases, palliative radiation may start within 24 hours of last dose of Debio 1347, unless, in the judgment of the Investigator, subject safety will require a longer washout period prior to palliative therapy and dosing of Debio 1347 may resume with the resolution of any radiation toxicity to ≤ Grade 1.
4. Chronic immunosuppressant (e.g., cyclosporine following transplantation or systemic [e.g., oral, intravenous (IV), intramuscular (IM), subcutaneous (SC)]) steroid dose equivalent to > 10 mg prednisone daily); however, a transient steroid dose equivalent to > 10 mg prednisone daily might be allowed after discussion with the Sponsor.
5. Fibroblast growth factor injections, cosmetics containing FGF.
6. Proton pump inhibitors.

If treatment with a prohibited medication is necessary, the subject will be withdrawn from the study after discussion with the Sponsor.

7.7.4. Reporting of Prior and Concomitant Therapy/Medications

Administration of medications to and therapies taken by the subject during the study period must be reported on the prior and concomitant medications page of the eCRF using the World Health Organization Drug Dictionary (WHO-DD) classification.

Information to be reported on the eCRF includes: i) international non proprietary name and the trade name, ii) dosage information (i.e. total daily dose, unit(s), frequency and route), iii) dates of administration, and iv) reasons for use.

8. STUDY ENDPOINTS, ASSESSMENTS AND PROCEDURES

8.1. Endpoints

8.1.1. Primary endpoint

ORR (defined as the proportion of subjects with a BOR of partial or complete response) as centrally measured by RECIST 1.1 criteria.

8.1.2. Secondary endpoints

1. DoR (defined as the time from the date of the initial partial or complete response to date of the first documented progression or death due to any cause).
2. DCR (defined as the proportion of subjects with a BOR of CR or PR or SD).

3. PFS (defined as the time from the start date of treatment to date of the first documented progression 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 TEAEs assessed by NCI-CTCAE v5.0 and SAEs.
6. Debio 1347 plasma exposure (C_{trough}, 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 ECG and PK matching time-points.

[redacted]

8.2. Assessments

As per Protocol Amendment Nº 2, the assessments and procedures plan defined in the study protocol (section 8.2) will no longer be in force and will be replaced by standard institutional care practice. Subjects must be followed up regularly (at least every two months) to assess the potential occurrence of safety events and conduct the safety laboratory analyses, as described in Table 8.1b.

Pregnancy, AEs, AESI, and SAE will be collected and documented in the study eCRF. The dedicated report forms should be completed by the Investigator and sent to the Sponsor as specified in section 9.2 of this Protocol.

Subjects showing clinical benefit may remain on treatment with Debio 1347 until a condition to stop treatment is met for the last subject in the study.

8.2.1. Assessment of FGFR fusion/rearrangement

8.2.1.1. Pre-screening

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. 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, prior to or during the 28-day screening period.

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.

8.2.1.2. Post-hoc confirmatory test

Tumor FGFR fusion/rearrangement will be confirmed by a central laboratory in case pre-screening is performed locally at the study site. Central analysis of FGFR fusion/rearrangement is not required for eligibility. Functional gene fusions involving FGFR1-3 and containing an intact FGFR kinase domain will be confirmed by RNA sequencing.

8.2.2. Efficacy Assessments

As per Protocol Amendment Nº 2, the efficacy assessments described in section 8.2.2 will no longer be be in force and efficacy data will not be collected. Central radiological review will no longer be performed. The patient will be followed for efficacy by the Investigator as per institutional practice.

8.2.2.1. Tumour assessments

Of note: An imaging review will be conducted by a central radiological review board to confirm the tumor assessments of all subjects enrolled in the trial regardless of response.

8.2.2.1.1. *Screening*

1. Subjects will be examined and the tumor staged using the appropriate system.
2. A CT scan or MRI of the involved regions and tumour assessment according to RECIST version 1.1 guidelines[47] (see Appendix B) will be performed. The choice of the radiological method will depend on the tumour site.

   For each subject, the same radiological method must be used throughout the study.

8.2.2.1.2. *On-treatment*

1. A CT scan or MRI and tumour assessment of the target/non target lesions will be performed according to RECIST version 1.1 guidelines[47] (see Appendix B) 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.
2. A CT scan or MRI and tumour assessment of the target/non target lesions will be performed according to RECIST version 1.1 in all subjects at the time of disease progression and/or EOT.

8.2.3. Safety Assessments

1. Adverse events will be monitored throughout the study as of signature of informed consent and will be graded according to NCI-CTCAE v5.0 (see Appendix C).
2. Demographics, medical history and height measurement will be collected at screening.
3. Physical examination, vital signs (BP and heart rate after at least 5 minutes of supine rest), rating of ECOG PS (see Appendix A) and weight measurement will be performed at:
   - **All clinical visits as part of the standard institutional practice**
   - **EOT/progression**
4. As per Protocol Amendment Nº 2, central ECG reading will not be performed. ECGs (with PR, RR, QRS and QTcF intervals) after at least 5 minutes of supine rest will be recorded as part of the ongoing safety assessments.
   - **All clinical visits as part of the standard institutional practice**
   - **EOT/progression**
5. As per Protocol Amendment Nº 2, central analytical laboratory testing will not be performed. Laboratory tests will also be conducted according to standard institutional practice to support the

ongoing safety assessments. Medical decisions regarding the subject and his/her treatment will be based on local laboratory safety results.
Of note: 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 will be recorded on the AE page of the eCRF.

a. **Hematology**
Complete blood count with differential (including ANC), hemoglobin and platelet count – *see time points in item b below.*

b. **Chemistry - ALWAYS 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.

- **All clinical visits as part of the standard institutional practice**
- **EOT/progression**

6. Urinary pregnancy test in female subjects of childbearing potential.
   - **All clinical visits as part of the standard institutional practice**
   - **EOT/progression**
7. Urinalysis (red blood cells/high power field [hpf], white blood cells/hpf, casts/hpf and protein).
   - **All clinical visits as part of the standard institutional practice**
   - **EOT/progression**
8. If visual disturbance is suspected, a complete ophthalmologic examination will be performed. The examination will be interpreted by a qualified ophthalmologist, including visual acuity testing, slit-lamp ophthalmoscopy and indirect ophthalmoscopy.
9. Medications or corrective medical actions required as part of the management of safety events will be collected in the appropriate eCRF safety forms. Existing concomitant medications and/or therapies at the time of occurrence of safety events will also be recorded in the eCRF.

[redacted]

8.2.5. Pharmacokinetic Assessments

Blood samples will be collected for the determination of plasma concentrations of Debio 1347 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** Cycle 2 **Day 28. The exact date/time of Debio 1347 administrations and PK sample collection will be recorded.**

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

[redacted]

[redacted] The concentration of Debio 1347 in plasma will be determined using a validated LC-MS/MS method [redacted].

Detailed instructions on sample drawing, handling and shipping to the central laboratory will be provided in a separate laboratory manual. After completion of the analysis (if applicable), the remaining PK samples may be stored for up to a maximum of 15 years after the end of the study and, if required, may be used for a retrospective examination of safety laboratory tests, of proteins involved in body disposition or the pharmacological effects of Debio 1347, for metabolic profiling or for further bioanalytical investigations (such as method cross-validation) to validate data for the development of Debio 1347.

8.2.6. [redacted], Tumour and [redacted] Assessments

[redacted]

8.2.6.2. Tumour biopsy assessments

A tumour biopsy will be collected at pre-screening/screening (if biopsy not possible adequate unstained archival slides or tumor block must be made available) for the assessment of predictive biomarkers and [redacted]. The biopsy may be also used to generate information needed for research and development of tests allowing to detect FGFR alterations.

[redacted]

As per Protocol Amendment Nº 2, no further tumor biospies will be collected at time of progression.

[redacted]

8.2.7. Follow-up Assessments

As per Protocol Amendment Nº 2, patients who discontinue study treatment will only undergo a safety follow-up (i.e. during 30 days post last Debio 1347 dose administration). Patients will not be followed for disease status and survival follow up. Sub-section "a" below applies exclusively. After treatment discontinuation (= EOT visit), subjects will be followed up for:

a. **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;

b. **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;

c. **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;

d. **Pregnancy screening** every 28 days for 6 months after the last Debio 1347 dose. All pregnancies detected during the 6-month post-EOT follow-up period should be reported according to the standard process described in Section 9.7

8.3. Study Procedures and Plan

Assessments are described in detail in Section 8.2. A study plan including timing of tests and evaluations is presented below in Table 8-1.

All eligible subjects will attend the study visits indicated in the study plan. Study procedures must be performed according to the planned time schedule with strict adherence to visit intervals.

Prior to conducting any of the screening tests, the Investigator or his/her designee will explain the study fully to the prospective subject and provide him/her with a copy of the Patient Information Leaflet/Informed Consent Form for the entire study. If the subject is willing to participate in the study, s/he and the Investigator or his/her designee will each sign two copies of the Informed Consent Form of which the subject keeps one.

Subjects who are confirmed at the pre-screening assessment as harboring FGFR fusions/rearrangements (see Section 8.2.1.1) will attend the full screening visit within 28 days prior to the first treatment cycle. Subject suitability will be confirmed by the inclusion/exclusion criteria in Section 6. A subject may be re-screened on the conditions described below.

Of note: Subjects who require a central assessment of FGFR status (pre-screening test, see Section 8.2.1.1) will be asked to sign a pre-screening Informed Consent Form to this intent.

As per Protocol Amendment Nº 2, the updated study plan is presented in Table 8-1b.

All subjects will be followed by the Investigator as per standard institutional care practice. Subjects will receive Debio 1347 for as long as they are benefitting from the study drug and there is no safety concern as per Investigator's judgment. Pregnancy, AEs, AESI, SAEs, will be documented and collected in the study eCRF, and reported using dedicated forms described in section 9.2 of this protocol.

8.3.1. Rescreening

In certain circumstances subjects may be re-screened for inclusion into the study despite an initial screening showing them to be ineligible, e.g.:

- A subject consented to participate, met the eligibility criteria but was delayed in starting due to a change in situation (i.e., family issues, request for attending a private matter, etc.).
- A subject failed eligibility due to an acute event that resolved or was stabilized with medications.
- Reversible causes of screening failure that were adequately treated, e.g., anemia precluding subject participation was treated by transfusion.

In these situations:

- A new eCRF will be used.
- A new identification number will be assigned to the subject.
- The subject will be flagged as having been re-screened in the eCRF and on the site master list.

- The eCRF will be completed with the new screening data; data from the initial screening must not be copied from the initial eCRF into the new eCRF; the latter must be completed based on the current clinical situation as documented by the subject's clinical notes.
- The subject may need to sign a new consent form as part of the screening procedure.

A subject who failed to meet the eligibility criteria in a first attempt should not be re-screened if no changes or treatments indicate that the subject may possibly be suitable.

Table 8-1 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]														
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 6.1).
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 asessments: 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.

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.
   4) [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 9.7

Table 8-2b 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 Nº2)	●		
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 Nº 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.

8.4. End-of-treatment and Overall End-of-study

8.4.1. End-of-treatment Criteria

Treatment with Debio 1347 will continue until any of the following occurs:

1. Subject withdraws consent. In this case, the subject will be discontinued from the trial and will be followed up according to the study plan.
2. Disease progression documented by CT scan/MRI, physical examination or any other method of evaluation or measurement~~.~~. An exception can be made for subjects who progress due to brain and/or bone metastases who may continue treatment with Debio 1347 if, in the Investigator's opinion, there is a reasonable evidence of clinical benefit. The Medical Monitor must be informed.
3. Unacceptable toxicity.
4. Pregnancy.
5. In the subject's interest as judged by the Investigator.
6. The Sponsor or Independent Ethics Committee (IEC) decides to terminate the study.

Subjects who are removed from study treatment due to AEs are to be treated and followed-up according to accepted medical practice and all pertinent information concerning the outcome of the treatment is to be recorded in the eCRF.

8.4.2. End-of-study Criteria

1. Withdraws consent.
2. Adverse event, e.g. intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree; or intercurrent illness that, in the opinion of the Investigator or the study Medical Monitor, compromises the subject's safety.
3. Subject non-compliance.
4. Subject lost to follow-up.
5. If, in the Investigator's opinion, continuation in the trial would be detrimental to the subject's wellbeing.
6. A major protocol violation occurs. If a minor protocol violation occurs, the Sponsor's Trial Manager will be contacted to discuss if the subject has to be withdrawn.
7. Prohibited medication as indicated in Section 7.7.3 is required/used during the course of the trial. In the event a subject is found to be taking a prohibited medication during the trial, the site should immediately contact the Medical Monitor. The decision to withdraw the subject will be made in conjunction with the Sponsor.
8. Non-drug related reason; e.g. subject relocates too far from study centre.
9. Sponsor or IEC decides to terminate the study.

8.4.3. Overall End-of-study

The study will be considered as completed 30 days after the last subject discontinued treatment.

9. ADVERSE EVENTS

The Investigator is responsible for detection and documentation of events meeting the criteria and definition of an AE/SAE as provided in this protocol. At each safety evaluation during the study, the Investigator or designee will collect information on unusual manifestations or AEs and SAEs, and will record them on the AE page of the eCRF. Their nature, severity, duration, treatment and relationship with the IMP(s) as assessed by the Investigator will be recorded. The Investigator will also indicate whether study treatment was disontinued and how the event evolved.

9.1. Definitions and Assessment Criteria

9.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse events are signs of illness (including abnormal laboratory findings) or symptoms occurring or worsening in the course of the study. Adverse events can be serious or non-serious. They may or may not lead to the withdrawal of the subject from the study.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry or urinalysis) or other safety assessments (e.g., ECGs, vital sign measurements…) including those that worsen from baseline and assessed to be clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- A medical or surgical procedure (e.g., endoscopy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing diseases(s) or condition(s) present or detected at the start of the study that do not worsen.

Reporting of disease progression: Disease progression/recurrence, symptoms and signs related to tumour progression/recurrence, e.g., hospitalisation due to a tumour progression, should not be reported as an AE or SAE

9.1.2. Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (i.e., puts the patient at immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;

  Of note: In general, hospitalization signifies that the subject has been detained (at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during

hospitalisation are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity;

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

- Is a congenital anomaly/birth defect, or
- Is otherwise medically significant: Important medical events that may not immediately be life threatening or result in death or hospitalisation, but that jeopardise the patient/subject or require intervention to prevent one of the outcomes listed in the definitions above shall also be considered as serious.

Non-serious: All AEs that do not correspond to the definition of SAE are considered as non-serious.

Reporting of disease progression: Disease progression/recurrence, symptoms and signs related to tumour progression/recurrence, e.g., hospitalisation due to a tumour progression, should not be reported as an AE or SAE.

9.1.3. Severity of Adverse Events

Adverse events will be graded according to the NCI-CTCAE v5.0 criteria.

Hyperphosphatemia, which is not included in the NCI-CTCAE v5.0, will be graded as follows:

1. Serum phosphate levels > ULN but < 5.5 mg/dL (~ equivalent to Grade 1);
2. Serum phosphate levels 5.5 - 6.9 mg/dL (~ equivalent to Grade 2);
3. Serum phosphate levels 7 - 9.9 mg/dL (~ equivalent to Grade 3, as this is the expected level at which soft tissue calcifications might develop);
4. Serum phosphate levels > 10 mg/dL with or without renal impairment (~ equivalent to Grade 4).

9.1.4. Relationship with the Investigational Medicinal Product(s)

The Investigator or designee will determine the relationship between the AE and the IMP(s) according to the following criteria:

Reasonable causal relationship:

A clinical event, including laboratory test abnormality,

- Where time relationship to drug administration is at least reasonable, and
- Where other causes (e.g., underlying disease) may not by themselves explain the event, and/or
- Where a clinically reasonable response occurs on withdrawal (dechallenge).

No reasonable causal relationship:

A clinical event, including laboratory test abnormality,

- Where time sequence to drug administration is not reasonable, or
- Where other causes (e.g., underlying disease) can by themselves provide plausible explanations.

9.1.5. Adverse Events of Special Interest

The following cardiac-related events will be considered as AEs of special interest (AESIs):

- Episodes of ventricular tachycardia or fibrillation,
- Syncope and seizures,
- AEs resulting in subject discontinuation from the study.

All of the above listed AESIs require appropriate reporting (including narrative summary) within 24 hours of becoming aware of the event.

The procedure for AESI reporting is outlined in Section 9.5 of the protocol.

9.2. Reporting of Serious Adverse Events to the Sponsor

9.2.1. Reporting during the study

The Investigator must notify the Clinical Research Organisation (CRO)/Sponsor **of all SAEs within 24 hours of awareness** by fax or email using the Debiopharm 'SAE Report form'.

1. When reported by fax, the 'SAE Report form' will be filled in and sent with the provided fax cover page entitled 'Serious Adverse Event Report transmittal form' to the following number: [redacted]
2. When reported by email, the 'SAE Report form' will be sent to the Sponsor at the following email address [redacted]

Notification of SAEs does not depend on their relationship with the IMP(s). All SAEs regardless of their relationship with the study drugs and occurring until the last study visit will be reported as described above.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

9.2.2. Reporting post-study

Any SAE occurring within 30 days of the last IMP administration will be reported by fax, email within 24 hours of SAE awareness as described in Section 9.2.1.

After this period, all unusal safety information or any safety information that appears to be related to Debio 1347 will be reported within 24 hours by fax [redacted], email [redacted]; new SAEs that are spontaneously reported by Investigators to the CRO/Sponsor will be recorded and regarded for expedited reporting purposes.

9.3. Follow-up of Serious Adverse Events

All SAEs, regardless of severity, must be followed up:

- To resolution (subject health has returned to his/her baseline status or all variables have returned to normal), or
- Until stabilisation of the event has occurred (the Investigator does not expect any further improvement or worsening of the event), or
- Until the event is otherwise explained regardless of whether the subject is still participating in the study.

Some events, such as metastases, are often ongoing; however, once these events have been determined by the Principal Investigator to be stable or chronic, he/she may consider the event to be resolved or resolved with sequelae.

The Investigator will notify the Sponsor of any follow-up information by fax or e-mail within 24 hours of new information awareness (see Section 9.2.1 above).

9.4. Procedure for Serious Adverse Event Notification to Independent Ethics Committees

If required by applicable local regulations, the Investigator will promptly notify the relevant IEC (in addition to the Sponsor) of any SAE (including post-study SAEs and follow-up information) that occurred at their site or was brought to their attention by the Sponsor. The Investigator will verify that the IEC acknowledges receipt of the notification.

9.5. Procedure for Reporting Adverse Events of Special Interest

For any AESI (as defined in Section 9.1.5) occurring during the clinical trial period, whether related or not to the study drug and whether expected or not, the Investigator must notify the Sponsor within 24 hours of awareness by fax or email using the SAE form as described in Section 9.2.1.

All AESIs, regardless of severity, must be followed-up until:

- Resolution (the subject's health has returned to the baseline status or all variables have returned to normal), or
- Stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event), or
- The event is otherwise explained whether the subject is still participating in the study or not.

Some events are often ongoing; however, once these events have been determined by the Investigator to be stable or chronic, s/he may consider the event to be resolved or resolved with sequelae.

The Investigator will notify the Sponsor of any follow-up information by fax or email within 24 hours of new information awareness as described above.

9.6. Determination of Expectedness - Reference Document

In the European Community, for regulatory reporting purposes, expectedness of an event will be assessed according to the applicable reference document.

Debio 1347: Investigator’s Drug Brochure, current version.

9.7. Pregnancies

Pregnancies should be avoided during the study. Any subject who nevertheless becomes pregnant must be followed-up until pregnancy outcome is known.

The Investigator must notify the Sponsor within 24 hours of awareness of any pregnancy occurring from date of Informed Consent until 6 months after EOT by fax or email using the Pregnancy Report Form.

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported in an expedited manner.

10. MONITORING AND STUDY COMMITTEES

10.1. Monitoring

The study Sponsor is Debiopharm International SA, Lausanne, Switzerland.

At mutually convenient times during the study, the Investigator will let Debiopharm or its representative review all eCRFs and related source documentation, i.e., subject office, hospital, clinic, and laboratory records.

At timely intervals and at the closing of the study, all IMPs will be accounted for and dispensing records made available to Debiopharm or its representative (see also Sections 7.3 and 7.6).

In case eCRFs require support information, Debiopharm may request copies of subject records or other source documents. All the necessary steps will then be taken to protect subject identity. Adherence to local and national laws governing protection of subject identity will be ensured.

Copies of all diagnostic imaging films used to determine subject status must be available for Debiopharm International SA and external consultants. If requested, copies of the above films are to be produced for the files of Debiopharm International SA.

10.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be assembled prior to study start and will be comprised of independent experts in the field of oncology and biostatistics. The DMC will be responsible for the review of safety and efficacy data during the course of the study. The DMC will perform the planned interim analysis at end of stage 1 and provide recommendations to the sponsor as defined in the DMC charter.

The roles and responsibilities of the DMC and meetings frequency will be defined in the DMC charter.

Following the implementation of Protocol Amendment Nº 2, the DMC is no longer required.

11. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The general data management and statistical plan described in this section is applicable to all patients enrolled in the trial since the study start date until the implementation of the Protocol Amendment Nº 2.

Following Protocol Amendment Nº 2, only safety data will be captured.

11.1. Sample Size

A basket two stage adaptive design[42] will be used to assess the efficacy of Debio 1347 in terms of ORR. 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.

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

11.2. Data Management and Handling

11.2.1. Data capture, verification, and validation

Data entry, verification and validation will be captured using an electronic data capture (EDC) system. EDC system is a web-based computerized system designed for the collection of clinical data in electronic format (electronic case report forms [eCRFs]) accessed via an Internet URL link.

EDC system accesses (username and password) will be provided upon completion and confirmation of prerequisite training. Username and passwords are personal and confidential and must not be shared.

The Investigator and/or designee will accurately, completely, and in a timely manner enter the required study data into the eCRFs. One eCRF will be completed for each subject.

Validation of eCRF data is performed by i) automatic EDC system checks and ii) other data review tools, such as data listings. Data validation may result in the generation of queries. A query is a request for further information or clarification which may lead to data change. All queries (automatic and manual) will be generated and tracked within the EDC system until resolution. Manual queries can be raised directly into the EDC system by the clinical study team depending on the assigned EDC role throughout the duration of the study.

CRA review, i.e., SDV (source data verification), is conducted on an ongoing basis and is confirmed in the EDC system. In general the CRA review is focussed on the quality and integrity of the eCRF data.

The data management review is conducted on an ongoing basis, includes the review of all automatic system generated queries and is confirmed in the EDC system. In general, the data management review is focussed on the completeness and coherency of the eCRF data, and also includes reconciliation of external data vs eCRF data.

Medical review is conducted on an ongoing basis. In general, this review is focused on the completeness and coherency of the safety data.

The EDC system's audit trail captures all eCRF data related activities such as data entry, data modifications, data verification, data lock, e-signatures etc.

The eCRF data will be extracted from the EDC system into SAS® datasets on a periodic basis and at defined study time points for statistical analysis.

11.2.2. Coding

Medical history, tumour characteristics and AEs will be coded per system organ class and preferred term using the last available version of the MedRA (Medical Dictionary for Regulatory Activities). Prior and concomitant medications will be coded per anatomical therapeutic chemical (ATC) class levels 2 and 4 using the last available WHO-DD.

11.3. Analysis Population

Intent-To-Treat Population

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

Safety Population

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

Modified Intent-to-Treat Population

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

Per Protocol (PP) population

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.

PK population

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

C-QT population

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

The window for matching ECG evaluation and PK sampling will be fully described in the statistical analysis plan.

11.4. Timing of Statistical Analysis

The statistical analysis will be performed at the following time points:

- 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 basket and a maximum of 13 subjects per basket will be required for the end of Stage 1 analysis.

  As per Protocol Amendment N° 2, this analysis will not be conducted due to the lower than expected antitumor activity reported during an initial statistical review of pooled data.

- 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 abreviated clinical study report (CSR).

- A final descriptive analysis focused on safety will be conducted after the last subject has completed the EOS visit.

11.5. Statistical Analysis

11.5.1. General analysis methods

The statistical analysis will be described in detail in a SAP. Any deviations from the SAP, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the final report.

Ordinal and continuous data will be presented in the form of descriptive statistics, as number of subjects, mean, standard deviation, minimum, Q1, median, Q3, maximum. In addition, for PK endpoints, the geometric mean, 90% confidence interval (CIs) on geometric mean, the standard deviation of the geometric mean, and geometric coefficient of variation (CV) % will be presented.

Categorical data will be presented using contingency tables with absolute and relative frequencies.

Baseline is defined as the last measurement prior to the first study drug administration.

All data analyses will be performed using SAS® statistical software and WinNonlin® Professional.

11.5.2. Handling of missing data

Missing data will not be imputed unless otherwise stated. Handling of missing tumour assessment is described in section .

For adverse events, partially missing dates will be imputed for the purpose of classifying an event as treatment-emergent, dates as collected will be presented in data-listings. Adverse events with completely unknown start dates will be considered as treatment emergent. In case of a missing start day, if the AE start month and year is the month and year of the first administration of stuy drug, the AE will be considered as treatment emergent, otherwise, the missing day will be replaced by the 1st. In case of missing start day and month, if the AE start year is the year of the first administration of stuy drug, the AE will be considered as treatment emergent, otherwise the missing day and month will be imputed by the January1st.

11.5.3. Interim analysis

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 basket and a maximum of 13 subjects per basket will be required for the end of Stage 1 analysis. ORR homogeneity will be assessed using a pre-defined cut-off for the critical value of the exact test for contingency tables. If homogeneity is declared, the next analysis steps will be conducted using combined data from all baskets; if heterogeneity is declared, data will be analyzed separately for each individual basket.

After homogeneity assessment, a futility analysis will be conducted (for all baskets combined in case of homogeneity or per individual basket in case of heterogeneity). Futility will be assessed using a pre-defined minimum number of responses required at end of Stage 1.

In case of homogeneity, the study will continue to Stage 2 if 3 or more responses are observed at end of Stage 1, otherwise the study will stop for futility.

In case of heterogeneity, futility will be assessed in each basket separately. Baskets with 1 or more responses at end of Stage 1 will be eligible to continue to Stage 2.

The interim analysis at end of stage 1 will be conducted by the DMC. At end of stage 1 The DMC will provide recommendation to continue or terminate the study for futility or to terminate individual cohorts for futility based on the criteria defined above.

Details on the roles and responsibilities of the DMC will be provided in the DMC charter.

Based on initial review and monitoring of efficacy data the interim analysis is cancelled.

11.5.4. Disposition of subjects, demographic and baseline data

Disposition of subjects screened and treated will be summarized with reasons for study and treatment discontinuation by cohort and overall.

Demographic and baseline data including age, gender, race, ethnicity, weight, height and BMI (body mass index) will be listed and summarized by cohort and overall. Baseline tumour characteristics, including primary location of tumour and tumour stage will be summarized by cohort and overall. Medical history will be summarized by system organ class and by preferred term.

11.5.5. Extent of exposure

Extent of exposure including treatment duration and number of cycles will be listed and summarized by cohort and overall.

Incidence of treatment interruption and dose reductions will be summarized by cohort and overall.

11.5.6. Efficacy

The ITT population will be the primary analysis population for efficacy analysis. Efficacy analyses will be repeated on the mITT population and the PP population as supportive analyses. The efficacy analysis will be conducted using centrally measured response as primary analysis and repeated on locally measured response as sensitivity analysis.

Best overall response is defined as the best confirmed response observed from first administration of study drug until disease progression. A PR or CR response needs to be confirmed in the following assessment performed at least 4 weeks later. For subjects who experience clinical progression, a radiological assessment will be performed to confirm the progression and the results of radiological assessement will be used in the efficacy derivation.

11.5.6.1. Primary efficacy endpoints

Objective response rate is defined as the proportion of subjects with a BOR of partial or complete response as centrally measured by RECIST 1.1 criteria.

The primary analysis will be conducted at the main analysis and the hypothesis tested will be according to the decision taken at interim analysis:

- Scenario 1: If the ORR homogeneity assumption is met at the interim analysis, then the hypothesis will be

  $H0: ORR \leq 15\%$ against $H1: ORR > 15\ \%$

  The statistical comparison will be conducted 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 interim analysis, then a decision will be made at the time of interim analysis to further continue the study with only 1 cohort or 2 cohorts. Then the hypothesis tested at final stage will be

  $H0: ORR \leq 15\%$ against $H1: ORR > 15\ \%$ in each chosen cohort

  - Scenario 2a: In the case 1 cohort has been selected the statistical comparison will be conducted using a one sided Binomial exact test at an alpha level of 5%.
  - Scenario 2b: In the case 2 cohorts have been selected the statistical comparison will be conducted using a one sided binomial exact test at a Bonferroni adjusted alpha level of 2.5% for each cohort.

As such, the overall FWER (family wise error rate) for the study will be 5%.

Objective response rate measured centrally using RECIST v1.1 will be summarized by cohort and overall using frequencies and percentages. The CI will be presented overall or by cohort. In addition, BOR will be tabulated by cohort.

A sensitivity analysis will be performed using ORR as assessed by the Investigator using RECIST v1.1. The analysis will be performed as for the centrally measured ORR.

11.5.6.2. Secondary efficacy endpoints

Disease control rate is defined as the proportion of subjects with a BOR of CR, PR or SD. Disease control rate will be summarized by cohort and overall using frequencies and percentages. The 95% clopper Pearson CI will be presented overall and by cohort.

Duration of response is defined as the time from the date of the first documented PR or CR to date of the first documented disease progression or death due to any cause, whichever occurs first. It will be calculated only for subject with a best overall response of CR or PR.

Progression-free survival is defined as the time from the start date of treatment to date of the first documented disease progression or death due to any cause, whichever occurs first. It will be expressed in months.

The following censoring rules will be applied on PFS and DOR for subject with no documented disease progression or death:

- 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.

Overall survival is defined as the time from the start date of treatment to date of death due to any cause. Subjects with no documented death will be censored at the last date known to be alive.

Duration of response, PFS and OS will be summarized using the Kaplan Meier method. Median survival time and the associated CI will be estimated. Duration of response rate and PFS rate at 6 month and 1 year, and OS rate at 1 year and 2 years and the corresponding CIs will be estimated using the Kaplan Meier method.

11.5.7. Safety

The safety analysis will be conducted in the safety population.

Adverse events

Treatment emergent adverse events are defined as AEs that start on or after the first administration of study drug and within 30 days of last administration of study drug.

Treatment-emergent adverse events, TEAEs related to study drug, TEAEs by severity, TEAEs leading to treatment discontinuation and SAEs will be tabulated and listed by MedDRA system organ class and preferred term.

All study deaths and reasons will be listed.

Laboratory parameters

Safety laboratory parameters and corresponding changes from baseline will be presented as descriptive statistics by cohort and overall by timepoint. Shift tables based on the NCI-CTCAE v5.0 toxicity grading (and ad hoc grading criteria for hyperphosphatemia) will be presented for each laboratory 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. Any clinically significant abnormalities in laboratory values will be listed.

12-lead ECG

12-lead ECG parameters and corresponding changes from baseline will be summarized by cohort and by visit as descriptive statistics.

The number (and percentage) of subjects satisfying the following conditions will be summarized by cohort and overall.

- 450 ms < QTcF ≤ 480 ms
- 480 ms < QTcF ≤ 500 ms
- QTcF > 500 ms
- An increases from baseline of > 30 ms and ≤ 60 ms
- An increases from baseline of > 60 ms
- QTcF > 500 ms or an increases from baseline of > 60 ms.

No central reading of the original ECGs will be performed. Central tendency, categorical and morphological analyses will be performed, if deemed applicable.

Other safety parameters

Vital signs and corresponding changes from baseline will be summarized by cohort and by visit as descriptive statistics.

ECOG PS will be presented as contingency tables by cohort and by time point.

Prior and concomitant medications and will be tabulated by ATC level 2 and 4 and by cohort.

[redacted]

[redacted]

[redacted] Pharmacokinetics

Individual Debio 1347 concentrations will be listed by gender, subject and time point. Concentrations will be summarized as the number of subjects, arithmetic mean, standard deviation, minimum, median, maximum, 25th percentile (Q1), 75th percentile (Q3), CV%, geometric mean, standard deviation of the geometric mean, geometric CV%, and 90% CI by time point and by cohort.

Graphic displays of plasma concentration vs time will be presented individually by subject and as arithmetic means ± arithmetic standard deviations using linear/linear scales and as geometric means ± geometric standard deviations using $\log_{10}$/linear scales.

Based on sparse sample plasma concentrations (that were defined by D-optimal design using the population PK model available so far), pharmacokinetic 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 modeling approach. Pharmacokinetic parameters will be listed by subject and summarized by cohort and overall as descriptive statistics. Inter- and intra-individual PK variability will be assessed by pooling data of this study with those of other clinical trial(s).

If deemed appropriate based on safety and efficacy outcome, relationships between exposure vs efficacy (clinical response and/or any tumor metrics) and safety may be evaluated. Notably, the C-QTcF relationship based on ECG and PK matching time-points may be analysed by linear mixed effects modeling. [redacted]

[redacted]

Subordinated to the safety and efficacy outcome and data availability, if applicable, the C-QTcF analysis will be fully described in the statistical analysis plan. Population PK data analysis (including covariate analysis if deemed appropriate), and,if applicable, exposure-response analyses for safety and efficacy will be described in separate analysis plans and reported separately in dedicated reports. If applicable, data may be pooled and analysed with data from other clinical trial(s).

[redacted]

12. SPONSOR AND INVESTIGATOR OBLIGATIONS

12.1. Good Clinical Practice and Declaration of Helsinki

This trial will be conducted in compliance with the ICH GCP guidelines and the ethical principles that have their origin in the Declaration of Helsinki (see Appendix D) and its subsequent amendments.

12.2. Independent Ethics Committee

The protocol and informed consent and any other relevant study documentation as outlined in the guidance document of Directive 2001/20/EC for this study must be reviewed and approved by an appropriate IEC which conforms to the Declaration of Helsinki (see Appendix D) and local laws prior to enrolment of participants into the study. A letter documenting IEC approval (in which the protocol title and number are specifically identified) and a list of IEC members and affiliations must be received by the Sponsor prior to initiation of the study.

Within 90 days of completion of the study (last subject, last visit) or 15 days of early termination of the study, the IEC will be informed of the end of the study by the Investigator, Sponsor or designee.

Every serious or unexpected AE that might affect subject safety must be brought to the attention of the IEC by the Investigator if required by his/her IEC regulations.

12.3. Institutional Review Board

The study protocol, informed consent and any other relevant study documentation must be reviewed and approved by an appropriate IRB that conforms to local laws prior to enrolment of subjects into the study. It is the responsibility of the Investigator to ensure that all aspects of the institutional review are conducted in accordance with local regulations and applicable ICH GCP. A letter documenting IRB approval (in which the protocol title and number are specifically identified) and a list of IRB members and affiliations must be received by the Sponsor prior to initiation of the study. The investigator is responsible for submitting an Investigator Progress Report to the IRB in time for the IRB to carry out review prior to the expiration date of the current IRB approval. This is required as long as the study is ongoing.

The IRB will be informed by the Investigator of the completion or early termination of the study.

Every serious or unexpected AE that might affect subject safety must be brought to the attention of the IRB by the Investigator. Similarly, every report from the Sponsor concerning an AE must be brought to the attention of the IRB by the Investigator.

12.4. Informed Consent

The Investigator or designee will ensure that signed informed consent* in accordance with the Declaration of Helsinki, local laws and all applicable regulatory requirements, is obtained from each potential subject prior to any study related procedure. The informed consent process will be documented.

Each subject will be given oral and written information in an easily understandable language describing the nature and duration of the study. This must take place under conditions where the subject has adequate time to consider the risks associated with study participation.

Two originals of the informed consent will be signed by the subject (and/or legal authorised representative [guardian, next of kin or other authorised individual] if applicable) and the Investigator or designee. One signed original will be given to the subject and one will be kept in the Investigator file at the study site.

*Exceptions to the above occur, when, for instance, a subject is not able to give consent (e.g., stroke trials, emergency indication). In such cases, the informed consent procedure must be described in detail, including the possibility to obtain delayed consent or consent from a relative or legal guardian. Applicable regulations must be strictly enforced and referred to.

12.5. Subject Confidentiality

The Investigator will ensure that subject reports and samples are identified only by a subject identifier to maintain subject confidentiality. All subject study records will be kept safely in an access controlled area. Identification code lists linking the subject names to identifiers should preferably be stored separately from subject records. Clinical information will not be released without written permission from the subject, except for monitoring by Regulatory Authorities or the study Sponsor.

12.6. Data Reporting and Electronic Case Report Forms

The Investigator and/or designee will accurately, completely and in a timely manner enter data resulting from execution of the protocol into eCRFs made available by the Sponsor via an EDC system, i.e., a web-based computerised system designed for the collection of clinical data in electronic format. One eCRF will be completed for each subject and must be electronically signed and dated by the Principal Investigator or the Co-investigator responsible for subject care during the study. Corrections in eCRFs will be recorded in an audit trail. The data will be extracted from the eCRF database periodically after interim and final database locks. At the end of the study, each site will be given a CD-ROM with all study data entered by EDC.

12.7. Retention of Data

The Investigator will maintain adequate study records including the CD-ROM or equivalent with electronically collected study data, medical records, laboratory reports, informed consent forms, drug disposition records, safety reports, information regarding participants who discontinued and other pertinent data, such as letters and administrative documents exchanged between the Sponsor and the centre. Records can be in paper or electronic format.

All study records must be retained by the Investigator for the maximum period of time authorised by the hospital, institution or surgery but in no case for less than **15 years** after study completion.

To avoid any possible errors, the Investigator must contact the Sponsor prior to the destruction of any study records or if leaving the institution where the study was conducted. The Investigator will notify the Sponsor in the event of accidental loss or destruction of any study records.

12.8. Deviations from the Protocol

The Investigator will not deviate from the protocol. In case of medical emergencies, the Investigator will use medical judgment and will remove the participant from immediate hazard. The Sponsor and the IEC/IRB will be notified regarding the type of emergency and course of action taken. Any permanent changes or deviations in the protocol will be validated in an amendment to the protocol.

For European studies: The amendment must be approved by the Sponsor and, if substantial as defined in directive 2001/20/EC, submitted for approval to the Health Authorities and IEC prior to being implemented. If the change implies a modification of treatment or subject evaluation tests, a new version of the informed consent form must be prepared and submitted for approval to Health Authorities and the IEC. The Sponsor will assume any responsibility or liability resulting from a change in the protocol, only if the change has been approved in writing by himself, the Health Authorities, and the IEC.

For IND studies: The amendment must be approved by the Sponsor and the IRB prior to implementation. If the change implies a modification of treatment or subject evaluation tests, a new version of the informed consent form must be prepared and submitted for approval to the IRB. The Sponsor will assume any responsibility or liability resulting from a change in the protocol, only if the change has been approved in writing by himself and the IRB.

12.9. Investigational Medicinal Product Drug Accountability

The Investigator must maintain accurate records of the IMP(s) received from the Sponsor. These records will include receipt and dispensing dates, and dates of return and/or destruction of unused supplies.

At trial termination, clinical supplies must be accounted for and a written clarification provided in case of discrepancies. All unused supplies must be properly destroyed at the study site or returned promptly to the Sponsor; written authorisation from the Sponsor must be obtained prior to destruction which must be documented.

When the above tasks are delegated to a Pharmacist, the Investigator remains ultimately responsible for the maintenance of accurate drug dispensing records.

12.10. Study Monitoring

At agreed upon times during the study and after the study has been completed, the Investigator will let Sponsor representatives periodically review the eCRF and corresponding office, hospital, and laboratory records (source documents) of each study subject. The eCRFs must be completed by the Investigator on a regular basis (within 3 working days after each subject visit) and prior to each monitoring visit.

Monitoring visits allow the Sponsor or a mandated CRO to evaluate study progress, verify accuracy and completeness of eCRFs, resolve any inconsistencies in the trial records, and ensure that all protocol requirements, applicable local laws, ICH guidelines and Investigator obligations are fulfilled..

12.11. Sponsor Audits

During the study or after the study has been completed, the Investigator will allow Sponsor representatives or external auditors to conduct an audit of the study. The purpose of the audit is to evaluate compliance with GCP guidelines, applicable regulations, the study protocol and the Sponsor's procedures, and to assess accuracy of the study data.

Before the audit, the Investigator will be contacted by the monitor to arrange a convenient time for the visit. Investigator and staff are expected to be present, co-operate with the auditors, and allow access to all subject records supporting the eCRFs, and other study-related documents.

12.12. Regulatory Agency Inspections

The Investigator may undergo a Regulatory Agency/IEC/IRB inspection during the study or after the study has been completed. The purpose of such an inspection is to conduct an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial.

The Investigator and staff are expected to be available for the inspection and allow access to subject records supporting the eCRFs and other study-related documents. If given advance notice of this inspection, the Investigator must contact the Sponsor immediately.

12.13. Disclosure of Results and Publication Policy

Results of this Phase II study will not be publicly disseminated or published until the study data are mature for the final analysis of the primary study endpoint (as defined by the protocol). The publications must be conform to the CONSORT guidelines.[49]

However, for the purpose of submission of abstracts to congresses, a draft version of the analysis report may be generated if the Sponsor's Statistician determines prior to abstract submission that the inconsistencies remaining in the database will not affect the conclusions of the study, and that the database can be cleaned and locked in sufficient time to enable the preparation of the final statistical report by the time of presentation. In this case, the abstract should clearly stipulate that the results are not definitive.

The publication of the results of ancillary studies (e.g., translational research) is authorized at any time provided they do not mention the primary and secondary study endpoints.

All publications reporting results of this Phase II study must be reviewed and approved by the Sponsor's Statistician and Medical Monitor in charge of the study. All publications reporting results of this study must be reviewed and approved by the first author and the Study's Steering Committee. The first author is responsible for ensuring that all co-authors have seen and approved the final version of the publication prior to submission. A written agreement with the intent to submit a publication must be reached between the Sponsor, the first author and the Steering Committee.

In accordance with the International Committee of Medical Journal Editors,[50] each author of the publication should have participated sufficiently in the work to take public responsibility for the content. All other contributors (clinicians, pathologists, …) who do not meet sufficient criteria for authorship will be acknowledged in the publication.

For the primary publication, the first author will be the Steering Committee member who will be the primary responsible for generating the first manuscript draft, followed by the other Steering Committee members. In principle, the last author will be a Steering Committee Chairman (if different from the first author). The Investigators who enrolled evaluable subjects in the trial will be included as co-authors up to the total number of co-authors allowed by the journal, according to their contribution to subject enrollment.

Coordinators of integrated translational research components of the study or pathologists responsible for the central pathology review that is part of the study also qualify as co-authors. Two Sponsor representatives will be co-authors. These two co-authors are usually the Statistician and the Medical Monitor who were in charge of and contributed to the study.

All Investigators who enrolled evaluable subjects into the study (i.e., clinicians) or contributed scientifically to the study (i.e., pathologists, collaborators from the same institutions, ...) will be acknowledged in the publication. The acknowledgement list should include the name of all participating institutions and the name of the clinicians and other scientists involved with the study at that institution. Whenever a study participant has moved from one institution to another in the course of the study, that participant is listed with the institution to which s/he was affiliated at the time of starting his/her participation to the study, with the mention "(now at [*new affiliation*])"

Sponsor staff that made a substantial scientific contribution to the study but are not co-authors should be mentioned in the acknowledgement section (i.e., data managers, clinical scientists, clinical trial managers).

The person who took the lead in conducting an ancillary study is the first author of the relevant publication. The Sponsor representatives who contributed to the analysis and publication, if any, will also be co-authors. The list of co-authors must be approved by the Study's Steering Committee and Sponsor.

12.14. Insurance Policy

The Sponsor will subscribe a liability insurance covering his and the Investigator's responsibility as well as the responsibility of any person involved in the conduct of the study, provided there is proper adherence to the protocol. An insurance certificate will be provided by the Sponsor to the IEC/IRB if required.

12.15. Premature Study Discontinuation

The trial may be prematurely terminated by the Sponsor, the Investigator or the IEC/IRB at any time. If the study is prematurely terminated, the Investigator must promptly inform the study subjects and ensure that they receive appropriate therapy and follow-up. All procedures and requirements pertaining to study closure as defined by the Sponsor will be carried out.

If the Investigator terminates the trial, s/he should promptly inform the Sponsor and the IEC/IRB and provide a detailed written explanation of the termination. If the Sponsor terminates the trial, the Investigator should promptly inform the IEC/IRB and provide a detailed written explanation of the termination. If the

IEC/IRB terminates the trial or suspends its approval, the Investigator should promptly inform the Sponsor and provide a detailed written explanation of the termination.

13. REFERENCES

1. Eswarakumar, V.P., Lax, I., and Schlessinger, J., *Cellular signaling by fibroblast growth factor receptors.* Cytokine Growth Factor Rev, 2005. **16**(2): p. 139-49.
2. Wang, Y. and Becker, D., *Antisense targeting of basic fibroblast growth factor and fibroblast growth factor receptor-1 in human melanomas blocks intratumoral angiogenesis and tumor growth.* Nat Med, 1997. **3**(8): p. 887-93.
3. Singh, D., et al., *Transforming fusions of FGFR and TACC genes in human glioblastoma.* Science, 2012. **337**(6099): p. 1231-5.
4. Williams, S.V., Hurst, C.D., and Knowles, M.A., *Oncogenic FGFR3 gene fusions in bladder cancer.* Hum Mol Genet, 2013. **22**(4): p. 795-803.
5. Nakanishi, Y., et al., *Mechanism of Oncogenic Signal Activation by the Novel Fusion Kinase FGFR3-BAIAP2L1.* Mol Cancer Ther, 2015. **14**(3): p. 704-12.
6. Seo, J.S., et al., *The transcriptional landscape and mutational profile of lung adenocarcinoma.* Genome Res, 2012. **22**(11): p. 2109-19.
7. Arai, Y., et al., *Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma.* Hepatology, 2014. **59**(4): p. 1427-34.
8. Wu, Y.M., et al., *Identification of targetable FGFR gene fusions in diverse cancers.* Cancer Discov, 2013. **3**(6): p. 636-47.
9. Parker, B.C., et al., *Emergence of FGFR family gene fusions as therapeutic targets in a wide spectrum of solid tumours.* J Pathol, 2014. **232**(1): p. 4-15.
10. Ang, C., *Role of the fibroblast growth factor receptor axis in cholangiocarcinoma.* J Gastroenterol Hepatol, 2015. **30**(7): p. 1116-22.
11. Borad, M.J., et al., *Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma.* PLoS Genet, 2014. **10**(2): p. e1004135.
12. Zehir, A., et al., *Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients.* Nat Med, 2017. **23**(6): p. 703-713.
13. Babina, I.S. and Turner, N.C., *Advances and challenges in targeting FGFR signalling in cancer.* Nat Rev Cancer, 2017. **17**(5): p. 318-332.
14. Helsten, T., et al., *The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing.* Clin Cancer Res, 2016. **22**(1): p. 259-67.
15. Stransky, N., et al., *The landscape of kinase fusions in cancer.* Nat Commun, 2014. **5**: p. 4846.
16. Xiang, L., et al., *Comprehensive analysis of targetable oncogenic mutations in chinese cervical cancers.* Oncotarget, 2015. **6**(7): p. 4968-75.
17. Graham, R.P., et al., *Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma.* Human pathology, 2014. **45**(8): p. 1630-1638.
18. Nakamura, H., et al., *Genomic spectra of biliary tract cancer.* Nat Genet, 2015. **47**(9): p. 1003-10.
19. Gallo, L.H., et al., *Functions of Fibroblast Growth Factor Receptors in cancer defined by novel translocations and mutations.* Cytokine Growth Factor Rev, 2015. **26**(4): p. 425-49.
20. Yaeger, R., et al., *Genomic Alterations Observed in Colitis-Associated Cancers Are Distinct From Those Found in Sporadic Colorectal Cancers and Vary by Type of Inflammatory Bowel Disease.* Gastroenterology, 2016. **151**(2): p. 278-287 e6.
21. Kim, S.Y., et al., *Acquired resistance to LY2874455 in FGFR2-amplified gastric cancer through an emergence of novel FGFR2-ACSL5 fusion.* Oncotarget, 2017. **8**(9): p. 15014.
22. Bao, Z.S., et al., *RNA-seq of 272 gliomas revealed a novel, recurrent PTPRZ1-MET fusion transcript in secondary glioblastomas.* Genome Res, 2014. **24**(11): p. 1765-73.
23. Costa, R., et al., *FGFR3-TACC3 fusion in solid tumors: mini review.* Oncotarget, 2016. **7**(34): p. 55924-55938.

24. Di Stefano, A.L., et al., *Detection, Characterization, and Inhibition of FGFR-TACC Fusions in IDH Wild-type Glioma.* Clin Cancer Res, 2015. **21**(14): p. 3307-17.
25. Parker, B.C., et al., *The tumorigenic FGFR3-TACC3 gene fusion escapes miR-99a regulation in glioblastoma.* J Clin Invest, 2013. **123**(2): p. 855-65.
26. Yoshihara, K., et al., *The landscape and therapeutic relevance of cancer-associated transcript fusions.* Oncogene, 2015. **34**(37): p. 4845-54.
27. Capelletti, M., et al., *Identification of recurrent FGFR3-TACC3 fusion oncogenes from lung adenocarcinoma.* Clin Cancer Res, 2014. **20**(24): p. 6551-8.
28. Theelen, W.S., et al., *FGFR1, 2 and 3 protein overexpression and molecular aberrations of FGFR3 in early stage non-small cell lung cancer.* J Pathol Clin Res, 2016. **2**(4): p. 223-233.
29. Wang, R., et al., *FGFR1/3 tyrosine kinase fusions define a unique molecular subtype of non-small cell lung cancer.* Clin Cancer Res, 2014. **20**(15): p. 4107-14.
30. The Cancer Genome Atlas Research Network, *Comprehensive molecular characterization of urothelial bladder carcinoma.* Nature, 2014. **507**(7492): p. 315-22.
31. Majewski, I.J., et al., *Identification of recurrent FGFR3 fusion genes in lung cancer through kinome-centred RNA sequencing.* J Pathol, 2013. **230**(3): p. 270-6.
32. Zheng, S., et al., *SOX2 expression is associated with FGFR fusion genes and predicts favorable outcome in lung squamous cell carcinomas.* Onco Targets Ther, 2015. **8**: p. 3009-16.
33. Lee, J.C., et al., *Identification of a novel FN1-FGFR1 genetic fusion as a frequent event in phosphaturic mesenchymal tumour.* J Pathol, 2015. **235**(4): p. 539-45.
34. Kurobe, M., et al., *Development of RNA-FISH Assay for Detection of Oncogenic FGFR3-TACC3 Fusion Genes in FFPE Samples.* PLoS One, 2016. **11**(12): p. e0165109.
35. Necchi, A., et al., *Comparison of Fibroblast Growth-factor Receptor Gene Alterations at the DNA versus Messenger RNA Level in Advanced Urothelial Cancer: Insights for Clinical Research.* Eur Urol Focus, 2017.
36. Ross, J.S., et al., *Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder reveals a high frequency of clinically relevant genomic alterations.* Cancer, 2016. **122**(5): p. 702-11.
37. Nakanishi, Y., et al., *The fibroblast growth factor receptor genetic status as a potential predictor of the sensitivity to CH5183284/Debio 1347, a novel selective FGFR inhibitor.* Mol Cancer Ther, 2014. **13**(11): p. 2547-58.
38. Vaslin, A., et al., *Characterization of two novel oncogenic FGFR2 fusions sensitive to the FGFR-selective inhibitor Debio 1347 in cholangiocarcinoma*, in *AACR Annual Meeting 2015*. 2015: Philadelphia, USA
39. Voss, M.H., et al., *Debio 1347, an oral FGFR inhibitor: Results from a first-in-human, phase I dose-escalation study in patients with FGFR genomically activated advanced solid tumors.* J Clin Oncol, 2017 **35** (15 suppl): p. 2500.
40. Turner, N. and Grose, R., *Fibroblast growth factor signalling: from development to cancer.* Nat Rev Cancer, 2010. **10**(2): p. 116-29.
41. Brooks, A.N., Kilgour, E., and Smith, P.D., *Molecular pathways: fibroblast growth factor signaling: a new therapeutic opportunity in cancer.* Clin Cancer Res, 2012. **18**(7): p. 1855-62.
42. Cunanan, K.M., et al., *An efficient basket trial design.* Stat Med, 2017. **36**(10): p. 1568-1579.
43. Mermel, L.A., et al., *Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America.* Clin Infect Dis, 2009. **49**(1): p. 1-45.
44. de Naurois, J., et al., *Management of febrile neutropenia: ESMO Clinical Practice Guidelines.* Ann Oncol, 2010. **21 Suppl 5**: p. v252-6.

45. Flowers, C.R., et al., *Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline.* J Clin Oncol, 2013. **31**(6): p. 794-810.
46. Liu, C., et al., *Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: Executive summary.* Clin Infect Dis, 2011. **52**(3): p. 285-92.
47. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
48. Ramanathan, R.K., et al., *Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group.* J Clin Oncol, 2008. **26**(4): p. 563-9.
49. Schulz, K.F., et al., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.
50. *Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication.* J Pharmacol Pharmacother, 2010. **1**(1): p. 42-58.

14. APPENDICES

Appendix A	ECOG Performance Status
Appendix B	RECIST criteria
Appendix C	NCI-CTCAE v5.0 criteria
Appendix D	World Medical Association Declaration of Helsinki
Appendix E	Hyperphosphatemia management guidelines
Appendix F	Dermatological toxicity prophylaxis and management guidelines
Appendix G	Hypercalcemia treatment guidelines

Appendix A: ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix B: RECIST Criteria

Please refer to RECIST guidelines version 1.1 (Eur J cancer. 2009; 45(2):228-247) by using the link below:

http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf

Appendix C: NCI-CTCAE v5.0 criteria

The NCI-CTCAE v5.0 criteria can be consulted at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix D: World Medical Association Declaration of Helsinki

The declaration of Helsinki can be consulted at:

https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf

Appendix E: Hyperphosphatemia management

These are suggested guidelines based on emerging data from studies testing FGFR inhibitors and from experience of participating Investigators and certified pharmacists. However, clinical judgment by the treating physicians and local SOC must be followed to decide which management is the best for each case of hyperphosphatemia.

A. Initial Treatment

Serum phosphorus levels	Intervention
5.5 – 6.9 mg/dL	Continue treatment with Debio 1347 at current dose AND start on sevelamer oral POWDER 1200mg three times a day (subjects may use tablets if preferred, but tends to have more gastrointestinal toxicity) AND Escalate to sevelamer oral POWDER or tablets 2400mg three times a day if tolerated. Reassess serum phosphorus within 7 days
≥ 7 mg/dL	**Hold treatment with Debio1347** Start sevelamer oral POWDER or tablets 2400mg three times a day Add treatment with lanthanum carbonate (Fosrenol®) 1g three times a day Reassess serum phosphorus level within 7 days: If serum phosphorus level < 5.5 mg/dL → resume Debio 1347 at same dose and recheck within 7 days of resumption

N.B.

- Sevelamer should be preferably taken in the mid of meals
- Lanthanum carbonate should be taken just after meals
- Sevelamer and lanthanum must be administered at least 2 hours after or 4 hours before Debio 1347

B. Second Modification on Treatment

Serum phosphorus level	Intervention
5.5 – 6.5 mg/dL	Continue treatment with Debio 1347 at a current dose AND Continue sevelamer oral POWDER or tablets 2400mg three times a day Introduce treatment with lanthanum carbonate (Fosrenol®) to 1.0g three times a day or increase to 1.5g three times a day Reassess serum phosphorus level within 7 days
6.6-6.9 mg/dL	Continue treatment with Debio 1347 at current dose AND Continue sevelamer oral POWDER or tablets 2400mg three times a day Introduce treatment with lanthanum carbonate (Fosrenol®) to 1.0g three times a day or increase the dose to 1.5g three times a day Add treatment with oral acetazolamide 250mg twice a day Reassess serum phosphorus level within 7 days
≥ 7 mg/dL	**Hold treatment with Debio 1347 – consider dose reduction** Continue sevelamer oral POWDER or tablets 2400mg three times a day Increase treatment with lanthanum carbonate (Fosrenol®) to 1.5g three times a day AND Add treatment with oral acetazolamide 250mg twice a day Reassess serum phosphorus level within 7 days: - If serum phosphorus level < 5.5 mg/dL → resume Debio 1347 with dose reduction

N.B.

- Sevelamer should be preferably taken in the mid of meals
- Lanthanum carbonate should be taken just after meals
- Sevelamer and lanthanum must be administered at least 2 hours after or 4 hours before Debio 1347
- Acetazolamide should be preferably taken just after breakfast and dinner

C. Subsequent Modifications

Serum phosphorus level	Intervention
> 5.5 mg/dL - 6.9mg/dL	• **If not already done**, maximize regimen to include: - Sevelamer oral POWDER or tablets to 2400mg three times a day - Lanthanum carbonate (Fosrenol®) to 1.5g three times a day - Oral acetazolamide 250mg twice a day • **If regimen already maximized**, consider dose reduction (without interrupting Debio 1347 assumption) Reassess serum phosphorus level within 7 days
≥ 7 mg/dL	Hold treatment with Debio1347 – dose reduction needed Maximize regimen to include: - Sevelamer oral POWDER or tablets to 2400mg three times a day - Lanthanum carbonate (Fosrenol®) to 1.5g three times a day - Oral acetazolamide 250mg twice a day Reassess serum phosphorus level within 7 days: - If serum phosphorus level < 5.5 mg/dL → resume Debio 1347 with dose reduction

N.B.

- Sevelamer should be preferably taken in the mid of meals
- Lanthanum carbonate should be taken just after meals
- Sevelamer and lanthanum must be administered at least 2 hours after or 4 hours before Debio 1347
- Acetazolamide should be preferably taken just after breakfast and dinner

D. General Recommendations

1. **In subjects whose serum phosphorus control improves after Debio 1347 dose reduction, de-escalation of the hyperphosphatemia treatment can be considered at the discretion of the Investigator. Subsequent to any such adjustment, serum phosphorus level should be reassessed within 7 days.**
2. **In case of subjects with hepatic or renal impairment, it is recommended not to change hyperphosphatemia treatment even in the case of Debio 1347 dose reduction.**

References:

1. J. Hutchinson et al. Lanthanum carbonate: safety data after 10 years. Nephrology 2016; 21:987-994.
2. M. Ketteler et al. Efficacy and Tolerability of Sevelamer Carbonate in Hyperphosphatemic Patients Who Have Chronic Kidney Disease and Are Not on Dialysis. Clin J Am Soc Nephrol. 2008; 3(4): 1125–1130.
3. M. Senatore, et al. Does concomitant administration of sevelamer hydrochloride and lanthanum carbonate modify the control of phosphatemia? Eur Rev Med Pharmacol Sci 2011; 15 (11): 1352-1354.

Appendix F: Dermatological toxicity prophylaxis and management

These are suggested guidelines based on emerging data from studies testing FGFR inhibitors and from experience of participating Investigators and certified dermatologists. However, clinical judgment by the treating physicians and local SOC must be followed to decide which management is the best for each case of dermatologic toxicity.

PARONYCHIA

Severity (CTCA v.4.03)	Intervention
Grade 0	Prophylaxis with urea 10-20% moisturizing cream twice daily Gentle skin care recommendation for the subjects: - Avoid repeated trauma or friction and pressure on nails and nail beds form manicuring, artificial nails, nail biting, hangnails, or removal of the cuticle - Always use protective cotton gloves for fingernails and vinyl gloves for prolonged contact with water such as for dish washing - Contact with detergents, toxic nail products (e.g., toluene and formaldehyde), and use of nail polish removers and hardeners should be restricted - Trim nails regularly and ensure that they are straight and short, and smooth the edges with a nail file - Apply topical emollients to cuticles and periungual tissues every day; nail lacquers can also be used to restrict water evaporation from the nail plate - Wear cotton socks and comfortable wide-fitting footwear
Grade 1 Nail fold oedema or erythema; disruption of the cuticle **or** **Grade 2** Localized intervention indicated ; oral intervention indicated (eg, anticbiotic, antifungal, antiviral) ; nail fold oedema or erythema with pain ; associated with discharge or nail plate separation ; limiting instrumental ADL	Continue treatment of Debio 1347 at current dose and monitor for change in severity Consider bacterial/viral cultures Consider treatment with oral antibiotics (e.g. Cefadroxil or Ciprofloxacin 500 mg twice daily for 10-14 days) and antiseptic soaks for at least 14 days* Reassess after 2 weeks (either by healthcare professional or subject self-report): 1. If reactions do not improve, re-consider bacterial/viral cultures and change oral antibiotics accordingly.
Grade 3 Surgical intervention or IV antibiotics indicated; limiting self-care ADL	Interrupt Debio 1347; obtain bacterial/viral cultures Continue treatment with systemic antibiotics; Consider dermatological evaluation; Consider nail avulsion. Reassess after 2 weeks: 1. If reactions worsen or do not improve, dose reduction per Principal Investigator clinical judgment may be necessary. 2. Treatment discontinuation should be reserved after dose reduction.

*Antiseptic soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day.
[Modified from Y. Balagula, M.E. Lacouture, and J.A. Cotliar, Dermatologic Toxicities of Targeted Anticancer Therapies. J Support Oncol 2010;8-149-161]

HAND FOOT SYNDROME

Severity (CTCA v.4.03)	Intervention
Grade 0	Prophylaxis with urea 10-20% moisturizing cream twice daily and after every hand wash
Grade 1 Minimal skin changes or dermatitis (eg, erythema, oedema, or hyperkeratosis) without pain. **or** **Grade 2** Skin changed (eg, peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting instrumental ADL	Continue treatment of Debio 1347 at current dose and monitor for change in severity Consider treatment with Clobetasol 0.05% cream or foam twice daily and control pain and/or inflammation with NAIDS twice daily (preferably a COX2 inhibitor such as Celecoxib 100 mg twice daily) Reassess after 2 weeks (either by healthcare professional or subject self-report)
Grade 3 Severe skin changes (eg, peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting self-care ADL	Interrupt treatment of Debio 1347 until severity decreases to grades 0-1 Continue treatment with Clobetasol 0.05% cream or foam twice daily and control pain and/or inflammation with NAIDS twice daily (preferably a COX2 inhibitor such as Celecoxib 100 mg twice daily) Reassess after 2 weeks: 1. If reactions worsen or do not improve, dose reduction per Principal Investigator clinical judgment may be necessary. 2. Treatment discontinuation should be reserved after dose reduction.

[Modified from Y. Balagula, M.E. Lacouture, and J.A. Cotliar, Dermatologic Toxicities of Targeted Anticancer Therapies. J Support Oncol 2010;8-149-161]

XEROSIS (DRY SKIN)

Severity (CTCA v.4.03)	Intervention
Grade 0	Prophylaxis with urea 10-20% moisturizing cream twice daily Fragrance-free detergents and soaps
Grade 1 Covering < 10% BSA and no associated erythema or pruritus **or** **Grade 2** Covering 10-30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Continue treatment of Debio 1347 at current dose and monitor for change in severity Continue moisturizer with urea 10-20% cream and consider adding a mid-potency topical steroid cream (i.e. Triamcinolone 0.1% cream or a steroid cream with equivalent potency) Reassess after 2 weeks (either by healthcare professional or subject self-report); if reactions worsen proceed to next step
Grade 3 Covering > 30% BSA and associated with pruritus; limiting self-care ADL	Interrupt treatment of Debio 1347 until severity decreases to grades 0-1 Consider treatment with topical steroid cream twice a daily (e.g. Triamcinolone 0.1% cream or a steroid cream with equivalent potency) Reassess after 2 weeks: 1. If reactions worsen or do not improve, dose reduction per Principal Investigator clinical judgment may be necessary 2. Treatment discontinuation should be reserved after dose reduction.

ALOPECIA

Severity (CTCA v.4.03)	Intervention
Grade 0	Consider prophylaxis with Minoxidil 5% daily
Grade 1 Hair loss of < 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage **or** **Grade 2** Hair loss of ≥ 50% of normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the subject desires to completely camouflage the hair loss; associated with psychosocial impact	Continue treatment of Debio 1347 at current dose and monitor for change in severity Consider dermatologic evaluation Reassess after 2 weeks (either by healthcare professional or subject self-report)
Grade 3 NA	NA

ORAL MUCOSITIS

Severity (CTCA v.4.03)	Intervention
Grade 0	NA
Grade 1 Asymptomatic or mild symptoms; intervention not indicated **or** **Grade 2** Moderate pain; not interfering with oral intake; modified diet indicated	Continue treatment of Debio 1347 at current dose and monitor for change in severity Consider Dexamethasone 0.5% mouthwash three times a day. Reassess after 2 weeks (either by healthcare professional or subject self-report); if reactions worsen or do not improve, proceed to next step.
Grade 3 Severe pain; interfering with oral intake	Interrupt treatment of Debio 1347 until severity decreases to grades 0-1 Continue treatment with Dexamethasone 0.5% mouthwash three times a day. Reassess after 2 weeks: 1. If reactions worsen or do not improve, dose reduction per Principal Investigator clinical judgment may be necessary 2. Treatment discontinuation should be reserved after dose reduction.

Appendix G: Hypercalcemia treatment

Subjects with asymptomatic hypercalcemia do not require immediate treatment if the calcium level remains < 12 mg/dL (3 mmol/L). However, the subject should be advised to avoid factors that can aggravate

hypercalcemia (such as thiazide diuretics, volume depletion, prolonged bed rest or inactivity, and a high calcium diet [> 1000 mg/day]).

Adequate hydration (at least 6 glasses of water per day) is recommended to minimise the risk of nephrolithiasis.

- *Moderate asymptomatic hypercalcemia (calcium between 12 and 14 mg/dL [3 to 3.5 mmol/L])*: The decision to treat with saline hydration and bisphosphonates is at the Investigator's discretion.
- *Higher concentrations of calcium > 14 mg/dL (3.5 mmol/L) or the presence of symptoms requiring more aggressive therapy*. In this case, it is suggested to treat with a three-pronged approach of isotonic saline (at an initial rate of 200 to 300 mL/hour that is then adjusted to maintain the urine output at 100 to 150 mL/hour), salmon calcitonin (4 IU units/kg) and concurrent administration of zoledronic acid (4 mg IV over 15 minutes) or pamidronate (60 to 90 mg over two hours).