Clinical Development

Protocol QBGJ398-301

A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine With Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Fusion/ Rearrangement: the PROOF Trial

Statistical Analysis Plan

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	adverse event
AESI	adverse event of special interest
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvic transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BICR	blinded independent central review
BOR	best overall response
CI	confidence interval
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
CR	complete response
DCR	disease control rate
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
EQ-5D	EuroQOL five dimensions questionnaire
FGFR2	fibroblast growth factor receptor 2
HR	hazard ratio
IPCW	inverse probability of censoring weighting
ITT	intent-to-treat
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MSI	microsatellite instability
OCT	Optical coherence tomography
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	PFS on subsequent therapy
PK	pharmacokinetic
PR	partial response
PT	preferred term
QLQ	quality of life questionnaire
QOL	quality of life
QT	measure of time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcB	QTc corrected by Bazett's formula
QTcF	QTc corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors

RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse events

1 INTRODUCTION

The purpose of this statistical analysis plan is to provide details of the statistical analyses that have been outlined within the protocol for study QBGJ398-301 dated of 27 July 2021 (version 4.0)**.**The scope of this plan includes the final analysis and outline of the interim analysis. The detailedplan for the interim analysis will be provided in a separate document. The analyses detailed withinthis plan will help to evaluate the efficacy and safety of the treatment with infigratinib for subjectswith advanced/metastatic or inoperable cholangiocarcinoma with fibroblast growth factor receptor2 (FGFR2) fusion/ rearrangement.

2 OBJECTIVES

2.1 Primary objective

The primary objective is to determine if treatment with infigratinib improves progression-free survival (PFS) per blinded independent central review (BICR) compared to treatment with gemcitabine and cisplatin in subjects with advanced/metastatic or inoperable cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion/ rearrangement.

2.2 Secondary objectives

The secondary objectives include:

- Determine if treatment with infigratinib improve overall survival (OS) compared to treatment with gemcitabine and cisplatin for subjects with advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 fusion/ rearrangement.

- Evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS.

- Further evaluate the efficacy in subjects treated with infigratinib versus gemcitabine and cisplatin by overall response rate (ORR), best overall response (BOR), duration of response and disease control rate (DCR) determined by BICR and by the investigator.

- Characterize the safety and tolerability of single agent infigratinib.

2.3 Exploratory Objectives

The exploratory objectives are not conducted due to the brief Clinical Summary Report (CSR).

3 STUDY DESIGN

This is a multi-center, open label, randomized, controlled Phase 3 study to determine if treatment with infigratinib improves PFS per BICR with supportive key secondary endpoint of OS compared to treatment with gemcitabine and cisplatin in subjects with advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 fusion/ rearrangement.

Subjects will be randomized in a 2:1 ratio to receive oral infigratinib administered once daily for the first 3 weeks (21 days) of a 28-day treatment cycle compared to a regimen of gemcitabine with cisplatin given on Days 1 and 8 of a 21-day cycle. Randomization will be stratified by locally advanced vs metastatic disease, geographic region (North America vs Western Europe vs Asia Pacific vs rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

During the treatment period, subjects will be radiographically evaluated every 8 weeks ±7 days from the first dose of study drug, regardless of drug interruption, for tumor response (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1). When the decision is made to discontinue study drug, subjects will complete an End of Treatment (EOT) visit, no later than 8 days from the decision to discontinue study drug, and a Safety Follow-up visit no more than 30 days after last dose of study drug. If a subject discontinues study drug for reasons other than centrally confirmed progressive disease (PD), a radiographic assessment should be conducted at the EOT visit, unless taken within the previous 4 weeks.

Subjects who discontinue study drug for centrally confirmed radiographic PD confirmed by BICR will be followed approximately every 3 months (via telephone or office visit) for survival status and new anticancertherapy information (subsequent therapy and progression/PFS2) until End of Study (EOS), defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment. Subjectswho discontinue study drug for reasons other than centrally confirmed PD will continue to have radiographic assessments every 8 weeks ±7 days until centrally confirmed radiographic PD. Thereafter, these subjects will be followed approximately every 3 months for survival status and use of anticancer therapy, as described above.

Sparse PK blood samples will be collected from all subjects in the infigratinib group at multiple time points, predose (C_{min} infigratinib) and 4 hours (±30 minutes) postdose (C_{max} infigratinib). Plasma concentrations of infigratinib and its metabolites (including BHS697 and CQM157) will be measured.

For a PK substudy, blood samples will be collected, at multiple time points (predose [C_{min} infigratinib], 4 hours [±30 minutes] postdose, and 24 hours postdose [±1 hour]) from the first 40 subjects who receive infigratinib. Plasmaconcentration of infigratinib and its active metabolites

will be measured, and PK parameters will be assessed.

Following radiographic PD confirmed by BICR, subjects randomized to the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib. Before these subjects receive any infigratinib, certain exclusion criteria must be rechecked (Protocol Section 6.2). Assessments performed within the past 30 days may be used to check these criteria. Subjects who cross over to infigratinib will evaluated for safety and OS.

3.1 Sample Size Considerations

Approximately 300 subjects with a likely or known activating FGFR2 fusion/ rearrangement determined by a central laboratory or local laboratory will be randomized in the study (2:1 randomization, with approximately 200 in the infigratinib group and 100 in gemcitabine with cisplatin group) and stratified by locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

The primary endpoint is centrally reviewed PFS (ie, PFS assessed by BICR). Assuming a PFS hazard ratio (HR) of 0.67 (median PFS 11.9 vs 8 months) (Valle 2010) comparing infigratinib to gemcitabine with cisplatin, with 228 PFS events required, the study will provide approximately 80% power to demonstrate that infigratinib improves the PFS per BICR compared to treatment with gemcitabine and cisplatin at a 2-sided significance level of 0.05. Assuming the test on PFS is significant, with 224 deaths observed, the study will provide 66% power to demonstrate that infigratinib improves OS compared to treatment with gemcitabineand cisplatin assuming an OS HR of 0.7 (median OS 16.7 vs 11.7 months) (Valle 2010).

The study employs a group sequential design with one interim analysis for futility planned for PFS. The primary analysis for PFS will be conducted after approximately 228 PFS events have been observed and the interim will be conducted when approximately 114 PFS events (~50% of 228) are observed. A fixed 2-sided significance level of 0.0001 will be spent at the interim analysis for PFS. A Lan-DeMets alpha spending function approximating O'Brien Fleming boundaries will be used for the interim non-binding futility and final boundaries.

One interim analysis and one primary analysis for OS are planned. The interim analyses for OS will be conducted at the primary analysis for PFS. The primaryanalysis for OS will be conducted after approximately 224 deaths have been observed. OS will only be tested if PFS is found to be significant. The Lan-DeMets spending function approximating the O'Brien-Fleming spending function will be used to calculate the significance boundaries.

With 42-month uniform enrollment, the study is projected to reach the planned number of PFS events (228) per BICR in approximately 54 months from randomization of the first subject. The OS event goal of 224 deaths is projected to be reached approximately 66 months from randomization of the first subject. The required sample size is estimated to be a total of 300 subjects, assuming that approximately 10% of subjects will drop out per year before a PFS or OS event.

4 STUDY ENDPOINTS AND COVARIATES

4.1 Endpoints

The primary endpoint is centrally assessed PFS (from date of randomization until date of progression as determined by BICR or death due to any cause, whichever is earlier).

The secondary endpoints are:

- OS (from date of randomization until date of death)
- PFS as determined by the investigator
- ORR assessed by BICR according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
- ORR assessed by the investigator according to RECIST Version 1.1
- BOR, disease control rate (partial response [PR] + complete response [CR] + stable disease [SD]), and duration of response (only for subjects who have a response) assessed centrally and by the investigator according to RECIST 1.1
- Type, frequency, and severity of AEs and serious AEs (SAEs), laboratory abnormalities, and other safety findings.

5 HYPOTHESES

No hypotheses will be tested due to the brief CSR.

6 DEFINITIONS

6.1 General

6.1.1 Investigational Product/Study Treatment/Study Drug

'Investigational product' or 'study treatment' or 'study drug' is used to reference infigratinib or gemcitabine or cisplatin.

6.1.2 Study Day 1 and Study Day

Study day 1 is defined as the day of the first administration of study treatment after randomization. Study day is calculated as the date of an event/measurement – the date of first study treatment administration + 1 if the event/measurement is on or after the date of the first study treatment administration; study day is calculated as the date of an event/measurement – the date of the first study treatment administration if the event/measurement is before the date of the first study treatment administration.

6.1.3 Baseline

In general, the baseline value will be considered as the last measurement observed prior to taking thefirst dose of study treatment. For ECG, if a set of triplet ECG are the last ECG collected prior to taking the first dose of study treatment, the average of the triplet ECG will be considered as baseline.

For subjects who are randomized and never receive study treatment, the baseline value will be the last assessment before randomization (on the day of or before randomization).

6.1.4 Subsequent anti-cancer therapy

Subsequent anti-cancer therapy includes any other anti-cancer therapy for cholangiocarcinoma that are received after a subject has ended study treatment. Subjects who are randomized to receive the treatment of gemcitabine and cisplatin and continue receiving gemcitabine only treatment are not considered to have received subsequent anti-cancer therapy. For subjects treated by gemcitabine with cisplatin, if cisplatin was dropped from the regimen and patients continue to be treated by gemcitabine only, it should not be considered as subsequent anti-cancer therapy. However, if cisplatin is replaced with another medication and patients are treated by this medication with or without gemcitabine, this should be considered as subsequent anti-cancer therapy.

6.1.5 On Treatment Period

On treatment period is defined as first administration of study treatment through 30 days after the last administration of study treatment inclusively.

6.1.6 Initial Treatment Phase

Initial treatment phase is defined as first administration of initial study treatment through the end of study for non-crossover subjects. For crossover subjects, initial treatment phase is defined as first administration of initial study treatment through the day before the first Infigratinib taken. This period phase is applied to all time to event endpoints, such as OS and PFS.

6.2 Efficacy

6.2.1 Overall Survival Time (OS)

OS is defined as the number of months from randomization to death (date of death - date of randomization + 1)/(365.25/12). Subjects who have not died (no record of death) or are lost to follow-up will be censored at the date of last known to be alive. Subjects who died or lost to follow-up during Crossover Period are censored at the start date of Crossover.

6.2.2 Progression free survival (PFS)

PFS are limited to the initial treatment phase. It is defined as the number of months from randomization to disease progression (PD) or death due to any cause, whichever is earlier. Events after subsequent anti-cancer therapy will still be included. Subjects who are still alive without documented PD will be censored attheir last valid tumor assessment. For subjects who have a PFS event after missing two or more consecutive scheduled tumor evaluation (i.e., the previous valid tumor assessment is >18 weeks prior to the event), their PFS will be censored at their last valid

tumor assessment. Subjects who have no qualified PFS event or any qualified post-baseline tumor assessment will becensored on their randomization date. PFS will be calculated per BICR and per investigator; PFSper BICR is the primary endpoint.

6.2.3 Best Overall Response (BOR)

BOR is defined as the best response a subject ever achieved after study treatment prior to any subsequent anti-cancer therapy, in descending order of precedence by confirmed CR, confirmed PR, SD, and PD. Confirmed CR and PR will be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks apart. In the case of SD, measurements must have met the SD criteria at least once post-baseline no less than 6 weeks from the randomization date.

BOR will be derived per central imaging review and per investigator.

6.2.4 Overall Response Rate (ORR)

ORR is defined as the proportion of subjects with BOR of either confirmed PR or confirmed CR among ITT population with measurable disease at baseline. All subjects who do not achieve BOR of either confirmed PR or confirmed CR will be considered non-responders.

ORR will be derived per central imaging review and per investigator.

6.2.5 Disease Control Rate (DCR)

DCR is defined as the proportion of subjects with BOR of either confirmed PR/CR or SD or non-CR/non-PD. DCR will be derived per central imaging review and per investigator.

6.2.6 Duration of Response (DOR)

DOR is defined as time from initiation of response (CR or PR) to PD or death. If subjects do not reach PD or death, the DOR is censored at the last valid tumor assessment. Subjects who never reach the response are not included in DOR analysis. DOR will be derived per BICR.

6.2.7 Progression Free Survival on Subsequent Therapy (PFS2)

PFS2 is calculated as the number of months from randomization to the disease progression on the subsequent therapy or death due to any cause, whichever is earlier, as determined by the investigator. Subjects who are still alive without documented disease progression on the subsequent therapy and subjects who are still alive without subsequent therapy will be censored at their last valid tumor assessment. For subjects who have a PFS2 event (PD or deaths) after missing two or more consecutive scheduled tumor evaluation (i.e., the previous valid tumor assessment is >18 weeks prior to the event), their PFS2 will be censored at their last valid tumor assessment. Subjects who have no qualified PFS2 event or any qualified post-baseline tumor assessment will be censored on their randomization date.

6.3 Safety

6.3.1 Concomitant Therapies

Concomitant therapies are defined as any medications (other than study treatment) and significant

other therapies (including surgery and radiotherapy) administered on or after the first administration day of study drug and up to last study administration day of study drug + 30 days (ie, during the on-treatment period).

6.3.2 Treatment Duration

Treatment duration will be calculated separately for each study treatment (gemcitabine/cisplatin/infigratinib). Treatment duration is defined as last dose date of the corresponding study treatment – first dose date of the corresponding study treatment +1 day.

6.3.3 Cumulative dose

The planned/actual cumulative dose will be calculated separately for each study treatment (gemcitabine/cisplatin/infigratinib). The planned cumulative dose for gemcitabine/cisplatin/infigratinib refers to the total originally assigned dose as per the protocol over the duration for which the subject is on the corresponding study treatment as documented in the Dose Administration eCRF (first dose date to the last dose date of the corresponding study treatment). The actual cumulative dose refers to the total actual dose administered.

6.3.4 Relative dose intensity

The relative dose intensity will be calculated separately for each study treatment (gemcitabine/cisplatin/infigratinib). The relative dose intensity for gemcitabine/cisplatin/infigratinib is defined as cumulative actual dose a subject received divided by the planned cumulative dose for the corresponding study treatment. For example, a subject takes infigratinib from day 1 to day 21 at 125 mg/day; then from day 29 to day 30 at 100mg/day, and end treatment afterward. The cumulative actual dose =21*125+100*2=2825 mg;the planned cumulative dose =21*125+125*2=2875 mg. The relative dose intensity = 2825/2875=98.3%.

6.3.5 Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an adverse event that occurs on or after the firstadministration of study treatment and within 30 days after the last administration of study treatment.

7 ANALYSIS POPULATION

The primary analyses for the efficacy endpoints will be based on the intent-to-treat (ITT) population. Safety analyses will be performed on the safety analysis.

7.1 Intent to Treatment population

The ITT population includes all subjects who are randomized. Subjects will be analyzed by the treatment group randomized to, regardless of the treatment received. This ITT analysis set will be the primary analysis set for efficacy.

7.2 Safety Analysis Population

The safety analysis population includes all subjects who are randomized and receive at least one dose of study treatment. Subjects will be analyzed by the treatment received.

7.3 Central Confirmed FGFR2 Fusion/ Rearrangement Population

Central confirmed FGFR2 fusion/ rearrangement population is a subset of ITT population and limited to only the subjects who are FGFR2 fusion/ rearrangement positive as determined by central laboratory. Key efficacy analyses will be repeated for this population.

7.4 Subgroup Analyses

The summaries of the primary and secondary efficacy endpoints may be performed for subgroups, as appropriate, defined by

- locally advanced vs metastatic disease
- geographic region (North America, Western Europe, Asia Pacific, and rest of the world)
- prior neoadjuvant/adjuvant treatment (yes/no)
- received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

In addition, potential interactions between treatment and each of the factors that define the subgroups will be investigated for the primary efficacy endpoint.

Summaries of treatment-emergent adverse events will be provided for subgroups defined by age (<65 vs. ≥65), sex, region, and race.

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Principles

In general, any values, such as those due to unit conversion, will be reported rounding to the same number of decimal places as the original data. Month or year converted from day will be reported rounding to one place after the decimal point.

In general, categorical variables will be summarized using counts and percent. Continuous variables will be summarized using number of subjects, mean, median, standard deviation, Q1, Q3, minimum, and maximum.

Time to event endpoints will be analyzed by Kaplan Meier (K-M) method. No statistical test will be conducted.

SAS statistical software, version 9.4 or later, will be used for all analyses.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

8.2 Handling of Missing Data

Partial dates will be defined as dates that are missing certain elements of the date field. This may include missing information for the month, day, or year, or two of these elements, but not all three. If all three elements are missing, it is completely missing. In principle, for adverse events (AE) start dates, only partial missing dates may be imputed, and no imputation should be done on

complete missing dates. An AE should be considered as on-treatment as long as there is no clear evidence to indicateotherwise.

Partial dates for AE where the start day is missing will be imputedas the first day of the month unless the start month of the AE is thesame as the month when the study treatment is initiated. In this case, the start day will be imputedas first dose date unless the AE ends before the date of the first study treatment administration, where the AE start date will still be imputed to the first day of the month (Appendix 10.1).

In general, unless otherwise specified, for all other partial missing dates, if assessment day is missing, day 15 will be imputed; if start day is missing, day 1 will be imputed; and if end day is missing, last day of the month will be imputed. No other imputation will be done if month or year is missing.

Any AEs with partial/missing dates will be displayed as such in the data listings.

8.3 Subject Accountability and Disposition

The number of subjects randomized into the study by treatment group and by stratum, in addition to the number of subjects included in each analysis set, will be summarized.

The number of subjects who have received study treatment in the ITT population, have ended the treatment, and the reason for ending treatment will be presented. The reason for discontinuing study will also be summarized.

8.4 Demographic and Baseline Characteristics

Summary statistics will be provided for demographics (age, sex, race, age group [<65 vs. ≥65 and <75 vs. ≥75], region and other baseline disease characteristics including FGFR2 fusion/ rearrangement status and fusion partner both by central and local, lymph node involvement,stage at initial diagnosis, time from initial diagnosis to randomization, and histology.

8.5 Medical history

A listing of medical history and current medical conditions will be provided, using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. Medical history will also be summarized by system organ class and preferred term.

8.6 Prior Anti-cancer therapy

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

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), setting at last regimen, whether subjects progress on or after last regimen. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include the total number of subjects who received prior anti-neoplastic radiotherapy, the radiotherapy locations, (including all locations

recorded for each patient), setting at last radiotherapy, radiotherapy type at last radiotherapy and whether subjects progress on or after last radiotherapy.

The summary of prior cancer-related surgery will include the time (in months) between the last surgery (non-biopsy procedure) to start of study treatment, and procedure at last surgery.

8.7 Protocol deviations

The number (%) of subjects with any CSR-reportable protocol deviation will be tabulated by the deviation category for the ITT population.

8.8 Efficacy Analyses

The primary efficacy analysis will be conducted on the intent to treat (ITT) population, which will include all subjects who are randomized. Subjects will be analyzed according to the treatment group that they are randomized to.

All primary and secondary efficacy endpoints will be summarized as specified in General Principle Section 8.1. The analysis of time to event endpoints such as PFS, OS and DOR is specified in Section 8.1.

All the efficacy analyses will be repeated for the central confirmed FGFR2 fusion/ rearrangement population asthe sensitivity analyses.

8.8.1 Sensitivity Analysis for PFS per BICR

As a sensitivity analysis, all tumor assessments per BICR and death after any subsequent anti-cancer therapy will be excluded from PFS per BICR derivation. PFS per BICR will be censored at last valid tumor assessment prior to any subsequent anti-cancer therapy if there is no PFS event prior to the subsequent anti-cancer therapy. The same analysis approach described in Section 8.8 for PFS per BICR will be applied.

8.8.2 Sensitivity Analysis for OS

Subjects in either arm may receive subsequent anti-cancer therapy other than the treatment they are randomized to. In this analysis, OS will be censored at the initialization of the first subsequent anti-cancer therapy.

8.9 Safety Analyses

Analysis of safety will be performed on the safety analysis population. In general, summaries will be provided only for the baseline and on-treatment safety assessments, which are the assessments taken during the on-treatment period.

For subjects in gemcitabine/cisplatin arm who cross-over to infigratinib, the summary of safety assessments described in Section 8.9.1 to Section 8.9.9 will be limited to the assessments within last dose of gemcitabine and cisplatin plus 30 days and prior to the initiation of infigratinib. The assessments on or after the initialization of infigratinib will be summarized separately as described

in Section 8.9.10.

8.9.1 Adverse Events

Treatment-emergent AEs (TEAEs) will be summarized. TEAEs include all AEs that start on or after the first dose day of the study treatment and up to last dose day of the study treatment +30 days. All AEs collected in the AE (e)CRF page will be listed with TEAE flagged.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with different CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

The following summary tables will be provided by treatment arm:

- Overview summary of TEAEs including the number and percentage of subjects with any TEAE, any serious TEAE, any TEAE leading to dose reductions/interruptions, any TEAE leading to discontinuation, and fatal TEAE.
- TEAEs by SOC and PT and worst grade
- Treatment related TEAEs by SOC and PT and worst grade
- Grade 3 or 4 TEAEs by SOC and PT and worst grade.
- Treatment emergent serious AEs (SAEs) by SOC and PT and worst grade
- Treatment emergent serious treatment-related AEs by SOC and PT and worst grade
- TEAE leading to study treatment discontinuation by SOC, PT, and grade
- TEAE leading to study treatment dose reductions by SOC, PT, and grade
- TEAE leading to study treatment dose delays by SOC, PT, and grade
- TEAE requiring additional medication or therapies by SOC and PT and worst grade
- TEAEs by PT by descending order of frequency
- Treatment related TEAEs by PT by descending order of frequency
- All TEAEs occurred in ≥10% subjects by PT by descending order of frequency
- Grade 3 or 4 TEAEs by PT in descending order of frequency
- Treatment related Grade 3 or 4 TEAEs by PT by descending order of frequency
- Treatment-emergent serious AEs (SAEs) by PT by descending order of frequency
- Treatment-emergent serious treatment-related AEs by PT by descending order of frequency
- TEAE leading to study treatment discontinuation by PT in descending order of frequency
- TEAE requiring additional medication or therapies by PT in descending order of frequency

The following listings will be produced:

- All adverse events

- All serious adverse events

The summaries of the subject incidence rates of TEAEs by system organ class and preferred term reported AEs will also be provided for subgroups defined by age, sex, and race.

Adverse events of special interest (AESI)

Each AESI consists of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). For each specified AESI, number and percentage of patients with at least one event within the AESI will be reported. AESI considered in this study include, but not limited to:

- Calcium phosphate homeostasis, including the subcategories of hypercalcemia, hyperphosphatemia, and hypophosphatemia
- Ocular disorder
- Tissue calcification
- Pathological fracture
- Vascular calcification/mineralization
- Keratitis Grade 3 or higher
- Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED)

For each AESI (or its subcategory), the overall summary of the characteristics will be provided. In addition, each AESI will also be summarized by subcategory (as applicable), preferred term and worst grade.

In addition, overdose as reported by investigator will be summarized. Potential drug induced liver injury that meets the following Hy's Law criteria will be summarized as part of laboratory summary.

Deaths

Primary reason for death will be summaries for on-treatment deaths (death occurs on treatment period), post-treatment death (death occurs after on treatment period) and all deaths for the safety analysis population.

All deaths will be listed for the safety analysis population, and on-treatment death will be flagged.

8.9.2 Concomitant Medications

Concomitant medications are defined as medications that subject have taken on treatment period. Concomitant mediations will be coded using the World Health Organization(WHODrug) dictionary and summarized by ATC class and preferred terms.

8.9.3 Treatment Exposure

Duration of studytreatment (last dose date – first dose date+1), cumulative dose, and the relative

dose intensity (cumulative actual dose/planned cumulative dose) will be summarized. For Gemcitabine/Cisplatin, the number of subjects with dose reduction/delay/permanently discontinued/dose re-escalation/infusion interruption will be summarized separately and the reason for those dose modification and infusion interruption will also be summarized. For infigratinib, the number of subjects with each of the prescribed dose change action taken and the reason for dose hold or dose reduced will be summaried. The summaryof the number of subjects with actual dose changes other than prescribed and the reason will also be summarized.

8.9.4 Laboratory Data Summary

Grade categorization of lab values will be assigned programmatically per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 or later. A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable.

The laboratory summaries will include all lab assessments collected within the last administration day of study treatment +30 days. Laboratory parameters for hematology and blood chemistry will be summarized at baseline, selected or each post-baseline visit (derived based on the visit schedule defined in the protocol), the maximum and minimum observed post-baseline values, and last observed value, along with the change from baseline. Lab shift tables will be done separately and labeled by direction. For example, sodium will be summarized as hyponatremia and hypernatremia.

In addition, number (%) of subjects with post-baseline laboratory abnormal results will be presented by grade for tests with CTCAE grading available and otherwise based on normal range. Incidence of potential drug-induced liver injury-based AST, ALT, TBL, AT, and bilirubin will be presented. Potential Hy's law cases will also be listed.

8.9.5 Ophthalmic assessment

Both visual acuity score (logMAR) and intraocular pressure (IOP) will be summarized at baseline, selected or each post-baseline visit (derived based on the visit schedule defined in the protocol along with a window), the maximum and minimum observed post-baseline values, and last observed value, along with the change from baseline.

Along with the summary described above, the number (percentage) of clinically significant changes in visual acuity score (logMAR) will be also summarized:

- <0.1 logMAR
- 0.1 - <0.2 logMAR
- 0.2 - <0.3 logMAR
- ≥0.3 logMAR

In addition, the number (percentage) of clinically significant values in tonometry will be summarized by visit:

- ≤21 mmHg

- >21 mmHg

Number (%) of clinically significant abnormalities will also be summarized by visit for slit lamp, OCT and fundoscopy exams.

8.9.6 Left Ventricular Ejection Fraction (LVEF)

Left ventricular ejection fraction (LVEF) will be summarized for baseline, selected or each post-baseline visit (derived based on the scheduled defined in the protocol along with a window), minimum post-baseline, along with the changes from baseline. Shift tables of the minimum post-baseline LVEF (<40%, 40% to 50%, ≥50%) with baseline LVEF status (≥50%, <50%) will be provided. Clinically significant changes of LVEF defined below will also be presented:

1. Absolute decrease from baseline >10% but <20% and LVEF ≥40% to <50%

2. Absolute decrease from baseline ≥20% and LVEF ≥20% to <40%

3. LVEF <20%

8.9.7 ECG

The ECG summaries will include all assessments available for the ECG parameter collected no later than 30 days after the last study treatment administration date.

ECG parameters will be summarized at baseline, selected or each post-baseline visit (derived based on the visit schedule defined in the protocol), the maximum and minimum observed post-baseline values, and last observed value, along with the change from baseline.

The number and percentage of subjects with notable ECG values will be presented.

- QT
    - New value of >500 ms
- QTcB, or QTcF
    - New value of >450 ms
    - New value of >480 ms
    - New value of >500 ms
    - Increase from baseline of >30 ms to ≤60 ms
    - Increase from baseline of >60 ms
- HR
    - Increase from baseline >25% and to a value >100 bpm

- Decrease from baseline >25% and to a value <50 bpm

- PR
  - Increase from baseline >25% and to a value >200 ms

- QRS
  - Increase from baseline >25% and to a value >100 ms

A listing of all ECG assessments will be produced by treatment and notable values will be flagged. In the listing, the on-treatment assessments will be flagged. In addition, a shift table baseline to worst on-treatment result for overall assessments will also be produced.

8.9.8 Vital signs and ECOG performance status

ECOG performance status will be summarized at baseline, selected or each post-baseline visit (derived based on the visit schedule defined in the protocol along with a window), the worst observed post-baseline values, and the last observed value, along with the change from baseline.

Vital sign assessments are performed to characterize basic body function. The following parameters should be collected: weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg). The vital sign summaries will include all assessments available no later than 30 days after the last study treatment administration date. The vital sign will be summarized at baseline, selected or each post-baseline visit (derived based on the visit schedule defined in the protocol), the maximum and minimum observed post-baseline values, and last observed value, along with the change from baseline.

8.9.9 Summary of Data After Cross-over

For subjects who cross-over to infigratinib, the number of subjects who consent to crossover, eligible to crossover, and exclusion criteria if not eligible will be summarized. End of infigratinib reason will also be summarized. Exposure to infigratinib and safety assessments after the first dose of infigratinib and within last infigratinib plus 30 days will be summarized. Baseline is the assessment last taken before the first dose of infigratinib.

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10 APPENDIX

10.1 Imputation of AE Start Date

Table 3. Imputation of AE start dates

Missing Element	Rule
day, month, and year	• No imputation will be done
day, month	• No imputation will be done
day	• If available month and year = month and year of study treatment start date then ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. ○ Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 01MONYYYY

10.2 TFL Shell

- 301 brief CSR TFL shell: in a separate document