Clinical Development

INFIGRATINIB

**Protocol CBGJ398X2204 Version 6 (Amendment 5)**

# A phase II multicenter, single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy

# STATISTICAL ANALYSIS PLAN (SAP)

Amendment 2

| | |
|---|---|
| Author: | PI |
| Version: | V3.0 (13 May 2020) |
| Supersedes: | V2.0 (26 March 2020) |

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# SUMMARY OF CHANGES (V1.0)

This Summary of Change summarized the change of the Statistical Analysis Plan for Study CBGJ398X2204 based on the SAP developed by Novartis dated on 09-Nov-2017.

**Rationale for Change**

The primary purpose of the changes is to:

- Revise the SAP to be consistent with the Protocol Version 5 (Amendment 4) (24-Apr-2019)
- Clarify some statistical analysis details

**Major Changes**

*Global changes*

- Editorial and format changes
- Change the term of 'patient' to 'subject' as appropriate
- Change the term of 'BGJ398' to infigratinib as appropriate
- Change the term of FMI v1 and FMI v3 to FMI I and FMI III, respectively
- Update the Protocol table/section numberings cited in this SAP to match with the corresponding tables/sections in the protocol
- Remove all the analyses related to the Bayesian approaches.

*Changes to specific sections*

- *Title page*: update SAP version set to Final V1.0 and update the date
- *Study design, Study objectives and endpoints*: updated to match with the protocol amendment 4 (24-Apr-2019)
- *Data analysis general information*: updated to match with the protocol on the scope and timing for the interim, primary and final analyses
- *Investigational drug and study treatment*: updated to match with the protocol on the introduction of new formulation of FMI IV; indicate that the analysis by treatment/formulation is determined by formulation a subject first received if a subject switches formulation during the study as required per the Protocol
- *Analysis sets*: clarify how analysis will be organized within Full Analysis Set (by treatment, by FGFR2 fusion/translocations status, etc); remove the Safety Set since it is overlapped with

the Full Analysis Set; clarify the definition of Per-Protocol Set; remove the section of Patient Classification; add Interim Analysis Set for Cohort 1 and Interim Analysis Set for Cohort 3; remove the section of Withdrawal of Informed Consent since it is not an analysis set; provide details on Subgroup of interest

- *Subject disposition*: clarify the summaries which will be provided for subject disposition.
- *Demographic*: The category of '18 - <65 years, 65 - <85 years and ≥ 85 years' is replaced with '<65 years vs >= 65 years'
- *Prior antineoplastic therapy*: clarify the summaries which will be provided for prior antineoplastic therapy
- *Protocol deviations*: clarify the categories of protocol deviations
- *Study Treatment*: indicate that no study treatment permanent discontinuation will be discussed in this section; remove several sections which provide too detailed programming specification; clarify the definition of treatment duration and relative dose intensity; specify that no summary will be provided for planned dose intensity and actual dose intensity; simply the algorithm for the summary of dose reductions and interruptions
- *Prior, concomitant and post therapies*: specify only on-treatment concomitant medication will be summarized; no general listing for concomitant will be provided.
- *Compliance*: the category of '< 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1' is replaced with '< =0.5, > 0.5 - <= 0.75, > 0.75 - <= 0.9, > 0.9 - <= 1.0 and >1.0'
- *Analysis of the primary objective*: specify that ORR per central review imaging will be the primary endpoint; clarify the timing for the interim and primary analysis for Cohort 1; delete all the analyses using Bayesian approaches; delete the subsection of Supportive analyses
- *Analysis of secondary objective(s)*: update to be consistent with the Protocol Amendment 4; add the description on best tumor burden change; provide details on the PFS censoring specification; provide the details on PFS sensitivity analysis; introduce the definition of PFS > 16 weeks for Cohort 2 and Cohort 3;
- *Safety objectives*: specify 'In general, summary will be provided only for the on-treatment safety assessments, which are the assessments occurring or taken during the on-treatment period'
- *Adverse Events*: emphasize that only TEAEs will be summarized; removed the summary tables related to TEAEs leading to study discontinuation; added some summary tables for TEAE; add the description of Adverse Events of Special Interest for this study
- *Laboratory data:* minor update on Table 2-3 and 2-4 and indicate the laboratory tests in those two tables are just examples; clarify the details on how laboratory data will be analyzed

- *Other safety data:* Add sections on Ophthalmologic assessment and Left ventricular ejection fraction (LVEF); clarify the analyses of ECG and cardiac imaging data and vital signs and ECOG performance status; for tolerability, the category of '<0.5, ≥0.5 - <0.75, ≥0.75 - <0.9, ≥0.9 - <1.1 and ≥1.1' is replaced with '<=0.5, >0.5 - <=0.75, >0.75 - <=0.9, >0.9 - <=1.0 and >1.0'

- *Pharmacokinetics*: update to indicate FMI IV will be used; Clarify that the sections on the PK analysis is intended to provide general principle for the PK analysis. Additional details of the analysis approaches will be provided in a separate PK analysis plan

- *Exploratory analyses*: indicate that the exploratory analyses will be conducted if there are sufficient data available

- *Interim Analysis*: specify the interim analysis for Cohort 1 and the interim analysis for Cohort 3

- *Sample size calculation*: update the rationale for Cohort 1 sample size based estimation precision (the Bayesian approach is removed); add the rationale for Cohort 2 and Cohort 3 sample size

- *Imputation rules*: Clarify the imputation rules for AE and CM start/end partial/complete missing date and the scope of the application of the imputation rules

# SUMMARY OF CHANGES (V2.0, Amendment 1)

This Summary of Change summarized the change of the Statistical Analysis Plan Version 2.0 for Study CBGJ398X2204 from Version 1.0 (29 May 2019).

**Rationale for Change**

The primary purpose of the changes is to:

- Revise the SAP to be consistent with the Protocol Version 6 (Amendment 5) (15-Jan-2020)

Global Changes

- Change the term of 'BGJ398' to infigratinib as appropriate

**Description of Changes**

- Title page: update SAP version and date and the corresponding protocol version and date
- Approval signature page: removed and a separate signature page will be used for approval
- List of Abbreviations: Add CSR/RPED
- 1 Introduction: update the corresponding protocol version and date
- 1.1 Study design: update to match with the current protocol
- Table 1-1: update to match the protocol
- Figure 1-1: replace with the one in the current protocol and the main change is from 'Cohort 1: ~120 patients, 108 with FGFR2' to 'Cohort 1: ~120 patients, 106 with FGFR2'
- 2.1 Data Analysis General Information: replace 'QED personnel' with 'QED Therapeutics'; indicate that one additional interim analysis will be added for Cohort 1; add details of the data review for Cohort 2 and Cohort 3
- 2.1.1.1 Investigational Drug and Study Treatment: add 'if subjects without FGFR2 fusion/translocation are included in the analysis' to clarify analysis details since only subjects with FGFR2 fusion/translocation will be included for the second formal interim analysis for Cohort 1.
- 2.2 Analysis Sets: update analysis sets used for the analyses mainly due to the change of adding the second interim analysis for Cohort 1
- 2.2.8 Subgroups of Interest: clarify the subgroups related to CYP3A4 inhibitors

- 2.3.3 Medical History: indicates a summary table of medical history will be provided instead of a listing.

- 2.4 Protocol Deviation: add 'Unless otherwise specified' since FAS will not be used for the second interim analysis for Cohort 1 after amendment 3

- 2.6 Analysis of Primary Objective: remove 'using FAS, or Interim Efficacy Analysis Set for Cohort 1' since different analysis sets will be used for different interim/primary/final analyses

- Best Overall Response and Disease Control in 2.7.1: add 'as specified by Cohort (Section 2.1)'

- 2.7.2 Safety Objectives: clarify the analysis sets which will be used for safety summary and listings.

- Deaths in 2.7.2.1.2: remove 'for the full analysis set' since the details on which analysis sets should be used for death listings have been clarified in the section of 'Safety Objective'

- Adverse Events of Special Interest in 2.7.2.1.2: to match the program wide definition: update the adverse events of special interest; add the section for 'Minimum Critical Toxicities'; add the section of 'phosphate binders medication'

- 2.7.2.2.1 CTC Grading for Laboratory Parameters: add details to clarify how grade 0 will be assigned.

- 2.7.2.2.1 Imputation Rules: clarify the algorithm of corrected calcium

- 2.7.2.2.3. Data Analysis: add 'as discussed in Minimum Critical Toxicities in Section 2.7.2.1.2' to provide analysis reference

- Table 2-3 Example of Laboratory Parameters for Which CTCAE Grades are Defined: update the table to be consistent with the analysis approaches

- Table 2-4 Examples of Laboratory Parameters (Without CTCAE Grades) for Which Lab Reference Ranges are Defined: update the table to be consistent with the analysis approaches

- 2.7.3 Other Safety Data: add a paragraph to provide overall guidance on the analysis

- 2.7.3.4 Vital Signs and ECOG Performance Status: clarify the summary of ECOG

- 2.7.4 Pharmacokinetics: replace "pre-dose and 2-hr post-dose" with "trough and 2-hour or 4-hour"; change 'Table 9 of CSP Amendment 4' to 'Table 10 of CSP Amendment 5'

- 2.7.4.3 Analysis Sets: Details added to match with the protocol

- 2.7.4.4 Basic Tables, Figures and Listings: Details added to match with the protocol

- Table 2-6 Non-compartmental pharmacokinetic parameters: update the table to match the protocol amendment 5
- 3.8.1.3.1 Analysis Sets: the section numbering is corrected to be 2.8.1.3.1; add ‘unless otherwise specified’
- 2.9 Interim Analysis: update the details of the interim analyses to match with the protocol amendment 5
- 3.1 Cohort 1: Two subjects who were considered previously as FGFR2 fusion/translocation subjects do not actually have FGFR2 fusion/translocation. Therefore, the number ‘74’ is changed to ‘72’ and ‘108’ is changed to ‘106’
- 5 Appendix: Add the following contents
- Table of Adverse Events of Special Interest, Search Strategies, and Rationales for Sponsor-Defined Search Strategies
- AESI: Calcium-phosphate homeostasis – hypercalcaemia, hyperphosphataemia and hypophosphataemia
- AESI: Eye Disorder of Central Serious Retinopathy/Retinal Pigment Epithelium Detachment
- AESI: Pathological Fracture
- AESI: Tissue Calcification
- AESI: Vascular Calcification / Mineralization
- AESI: Eye Disorder: SOC Eye Disorders (Excluding 9 PTs Used to Characterize CSR/RPED)
- Minimum Critical Toxicities
- CYP3A4 Inhibitors and Inducers
- Phosphate Binders
- 6 Reference: add one more reference

# SUMMARY OF CHANGES (V3.0, Amendment 2)

This Summary of Changes summarized the change of the Statistical Analysis Plan Version 3.0 for Study CBGJ398X2204 from Version 2.0 (26 March 2020).

**Rationale for Change**

The primary purpose of the changes is to:

- More precisely specify analysis methods for overall response rate (ORR), time to response (TTR), and duration of response (DOR).

**Description of Changes**

- Title page: updated SAP version, amendment number, and date; replaced PI with PI
- Summary of Changes: Added version and amendment numbers for clarity, as appropriate.
- Section 2.6.1: Added paragraph to specify analysis methods.
- Section 2.6.2: Removed the last sentence (related to Section 2.6.1 change above).
- Section 2.7.1: Added paragraph to specify analysis methods and deleted last sentence.
- Throughout: Reformatted to be in the current QED template and style guide, including revising table and figure numbers, adding appropriate headings to appear in the Table of Contents (eg, List of Abbreviations, Summary of Changes), completing the List of Abbreviations, defining abbreviations on first use only, appropriately referring to sections, and other minor editorial/administrative changes.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ATC | Anatomical Therapeutic Chemical |
| AUC | area under the curve |
| bid | bis in diem/twice a day |
| BLQ | below the limit of quantitation |
| BOR | best overall response |
| cfDNA | cell-free DNA |
| CI | confidence interval |
| CR | complete response |
| CSR | Clinical Study report |
| CSR/RPED | central serious retinopathy/retinal pigment epithelium detachment |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DOR | duration of response |
| FAS | full analysis set |
| eCRF | electronic Case Report Form |
| LVEF | left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| NCI | National Cancer Institute |
| o.d. | once daily |
| ORR | overall response rate |
| OS | overall survival |
| PD | pharmacodynamics |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PPS | per-protocol set |
| PR | partial response |
| PT | Preferred Term |
| qd | qua'que di'e / once a day |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SOC | System Organ Class |
| SMQ | Standardized MedDRA Queries |
| TEAE | treatment-emergent adverse event |
| TFLs | tables, figures, listings |
| TTR | time to response |
| WHO | World Health Organization |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CBGJ398X2204 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the ADaM Reviewer's Guide. This version of the SAP is based on the Clinical Study Protocol (CSP) CBGJ398X2204 Version 6 (Amendment 5) dated on 15-Jan-2020.

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

The SAP, TFL shells, and ADaM Reviewer's Guide documents may also serve as a reference for the creation of any outputs required outside of the CSR, eg, IB updates, abstracts, posters, presentations, manuscripts, and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

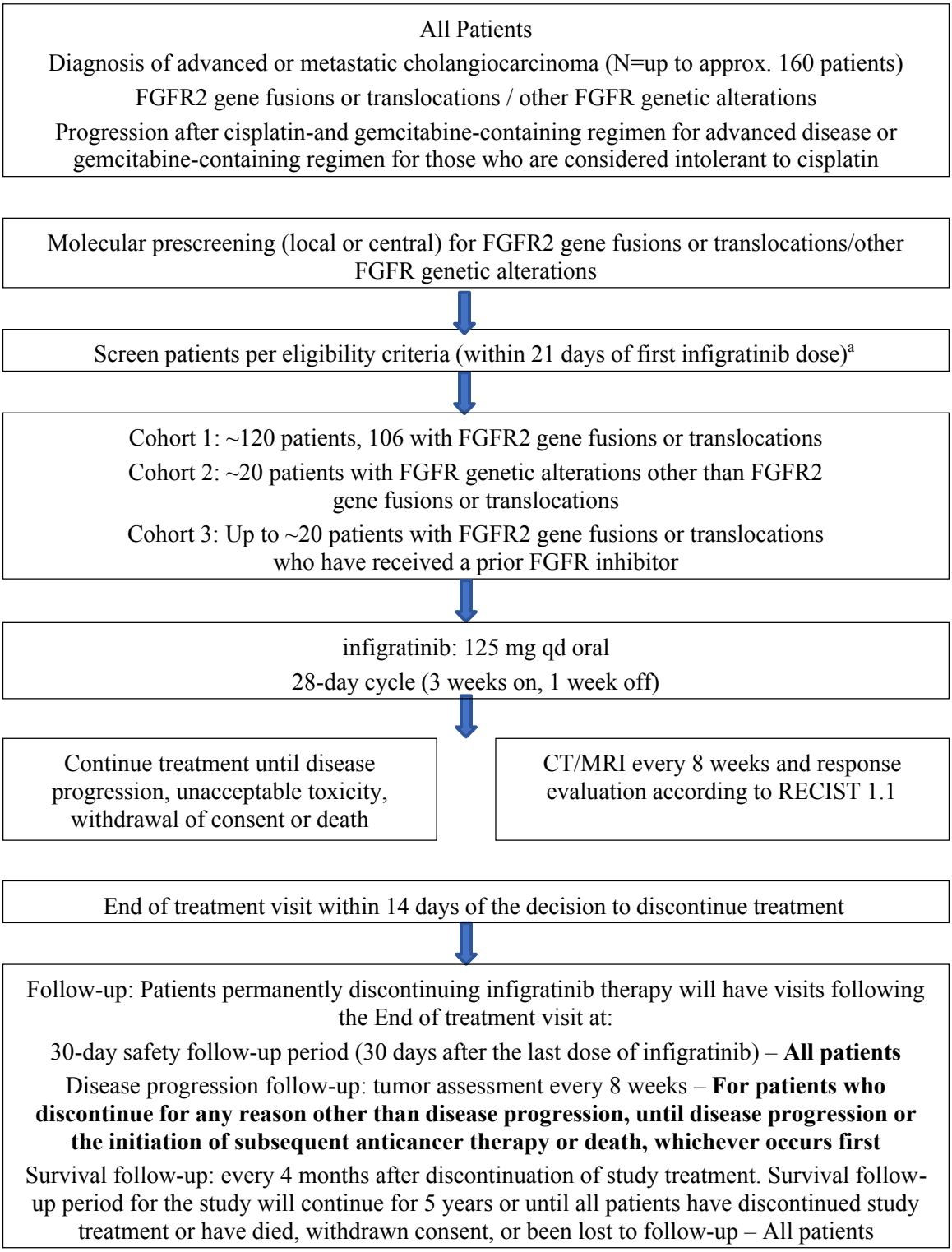
The purpose of sections 1.1 to 1.2 is to make the SAP a standalone document and to be more specific on endpoints as required. No clinical background information needs to be included, as this is already provided in the CSP; only information relevant to the analyses is to be included.

## 1.1 Study Design

This is a multi-center, open label, phase II study evaluating infigratinib anti-tumor activity in advanced or metastatic cholangiocarcinoma patients with FGFR genetic alterations. All patients will receive infigratinib once daily on a three week on (21 days), 1 week off (7 days) schedule in 28-day cycles. Approximately 120 patients in total will be enrolled into Cohort 1 on the study. As of Amendment 2, only patients with advanced or metastatic cholangiocarcinoma with FGFR gene fusions/translocation will be enrolled into Cohort 1. As of Amendment 4, two new cohorts, Cohort 2 and Cohort 3, were added to this study. Cohort 2 is planned to enroll approximately 20 patients with FGFR genetic alterations other than FGFR2 gene fusions or translocations and Cohort 3 is planned to enroll up to approximately 20 patients with FGFR2 gene fusions or translocations who have received a prior FGFR inhibitor other than infigratinib. According to Amendment 2, the final market image version 3 (FMI III) formulation of infigratinib replaced FMI I. According to amendment 4, the final market image version 4 (FMI IV) formulation of infigratinib will be used for patients in Cohort 2 and 3. Patients who started treatment prior to the implementation of amendment 2 should continue to receive the formulation of infigratinib that they received at the initiation of treatment until FMI IV is available at the study site. Pharmacokinetics, safety, and tolerability data from all available patients enrolled in either Cohort 2 or Cohort 3 treated with FMI IV up to the end of cycle 1 of treatment will be assessed and compared with the historical data from patients treated with FMI III.

In order to assess the antitumor activity of infigratinib, patients in all cohorts will be evaluated for tumor response radiographically every 8 weeks until disease progression or discontinuation from study using RECIST 1.1 criteria.

**Figure 1: Study Design (Applied to Protocol Version 6 (Amendment 5))**




[a] Screening assessments are to be completed within 21 days prior to the first dose of treatment, except for the radiological tumor assessment, which can be performed within 28 days prior to the first dose.

## 1.2 Study Objectives and Endpoints

Objectives and related endpoints are described in Table 1 below.

**Table 1: Objectives and Related Endpoints for Cohort 1 and Overall Study**

| Objective | Endpoint |
|---|---|
| **Primary (Cohort 1)** | |
| To evaluate the efficacy of single agent infigratinib in patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocations or other FGFR genetic alterations | Overall response rate (ORR) assessed by central imaging review as per RECIST v1.1 |
| **Secondary** | |
| Cohort 1: To further evaluate the efficacy of single agent infigratinib | Overall response rate assessed by investigator; progression free survival, best overall response, and disease control rate assessed by investigator and by central imaging review as per RECIST 1.1; and overall survival |
| Cohort 1: To characterize the safety and tolerability of single agent infigratinib | Safety: Type, frequency, and severity of AEs and SAEs; Tolerability: dose interruptions, reductions and dose intensity |
| **Overall study:** | |
| To determine selected trough and 2-hr or 4-hr plasma concentrations of infigratinib and its metabolites<br>To characterize the pharmacokinetic profile of infigratinib FMI III and FMI IV formulations | Selected trough and 2-hr or 4-hr plasma concentration profile and derived PK parameters of infigratinib and its metabolites<br>For FMI III and FMI IV: Plasma concentration profile and derived PK parameters of FMI III and FMI IV |
| **Exploratory (Overall Study)** | |
| To assess markers that may correlate with genetic alterations in tumor tissue at baseline, predictions of response and/or resistance (e.g. gene mutations, amplifications, deletion and/or altered protein expression or activation) | DNA sequencing of paired biopsies (tumor tissue) from patients who progressed and analysis of cell free tumor DNA<br>Serial serum CA19-9 levels |

**Table 2: Objectives and Related Endpoints for Cohort 2 and 3**

| Exploratory Objectives | Endpoint |
|---|---|
| To characterize the safety and tolerability of infigratinib in patients with advanced or metastatic cholangiocarcinoma with…<br>Cohort 2: …FGFR genetic alterations other than FGFR2 gene fusions or translocations<br>Cohort 3: …FGFR2 gene fusions or translocations who have received prior FGFR inhibitors | Safety: Type, frequency, and severity of AEs and SAEs; Tolerability: dose interruptions, reductions, and dose intensity |
| To evaluate the efficacy of single agent infigratinib in patients with advanced or metastatic cholangiocarcinoma with…<br>Cohort 2: …FGFR genetic alterations other than FGFR2 gene fusions or translocations<br>Cohort 3: …FGFR2 gene fusions or translocations who have received prior FGFR inhibitors | Progression free survival, overall response, best overall response, response onset, and disease control assessed by investigator as per RECIST v1.1, and overall survival |

# 2 STATISTICAL METHODS

## 2.1 Data Analysis General Information

Study data will be analyzed by QED Therapeutics and/or designated CRO(s) using the most updated SAS® version in the statistical computing environment. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 7.0 or higher.

Two formal interim analyses for Cohort 1 are planned after Amendment 3 as described in Section 2.9. The first formal interim analysis will include all patients in Cohort 1 who receive study treatment before the interim analysis cutoff date. The efficacy analysis for the first formal interim analysis for Cohort 1 will be focused on the population as described in Section 2.2.2 below. The second formal interim analysis will be conducted on all the subjects with FGFR2 fusions or translocations in Cohort 1. The primary analysis for Cohort 1 will be conducted when all patients in Cohort 1 have the potential to be followed for at least 10 months after their initial exposure to study treatment. For the interim and primary analyses for Cohort 1, patients will be grouped by fusion status (if subjects without FGFR2 fusions or translocations are included) and formulation. Here, the formulation refers to the first formulation a subject received if a subject switched formulation during the study as described in Section 1.1.

For Cohorts 2 and 3, review of data will be performed after a total of 15 patients in either Cohort 2 or 3 have been treated with FMI IV for at least one cycle. Primary analysis will be conducted when all patients in the cohorts have the potential to be followed for at least 10 months after their initial exposure to study treatment. Additionally, for Cohort 3, one interim analysis will be conducted after the first 10 dosed patients in this cohort have the potential to complete their second scheduled scans (approximately 16 weeks from their first dose) to determine if the cohort will be expanded.

The additional data for patients continuing to receive study treatment or remain in study past the data cutoff date of the primary analysis, as allowed by the protocol, will be reported in a final CSR that will be prepared at the end of the study. In the final CSR, analyses will be done for each cohort, for patients enrolled in Cohort 1 who do not have FGFR2 fusions or translocations, data may be combined and summarized with Cohort 2.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) and pharmacodynamics (PD) measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Additional data for which there is a separate informed consent, eg, PK, biomarker etc., collected in the clinical database without having obtained that consent will not be included in the analysis.

**Qualitative data** (eg, gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

**Quantitative data** (eg, age, body weight, etc.) will be summarized by appropriate descriptive statistics (ie, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

### *2.1.1 General Definitions*

#### *2.1.1.1 Investigational Drug and Study Treatment*

**Investigational drug** will refer to infigratinib as an oral formulation. The terms investigational drug and study drug/treatment are used interchangeably. For consistency across studies, the term study treatment will be used throughout this document.

**Table 3: Dose and Treatment Schedule**

| Study treatment | Formulation | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|---|
| infigratinib | FMI I<br>FMI III<br>FMI IV | Capsule(s) for oral use | 125 mg (administered as one 100 mg capsule and one 25 mg capsule) | Daily (3 weeks on, 1 week off schedule in 28-day cycles) |

A **treatment** is defined by the dose formulation (FMI I, FMI III and FMI IV). The treatment formulation is determined by the formulation a subject first received if a subject switches formulation during the study as described in Section 1.1.

Unless otherwise specified, all efficacy related analyses will be done separately for all patients, patients with baseline FGFR2 gene fusion/translocation, and patients with other FGFR genomic

alterations if subjects without FGFR2 fusion/translocation are included in the analysis. In addition, within patients who had baseline FGFR2 gene fusion/translocation, the data will be summarized by treatment. Unless otherwise specified, for all other analyses, including safety, disposition, demographic/baseline disease characteristics, study drug exposure and prior/concomitant/post therapy related analyses, will be done separately for all subjects, all subjects by FGFR status (FGFR2 gene fusion/translocation vs. other FGFR genomic alterations) if subjects without FGFR2 fusion/translocation are included in the analysis, and all subjects by treatment.

Note that reporting by treatment is equivalent to reporting by formulation, and "by treatment" will be used throughout this document.

#### *2.1.1.2 Date of First/Last Administration of Study Treatment*

In the single agent arm, the date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of infigratinib was administered and recorded on the Dosage Administration Record (DAR) eCRF. If a subject has not ended treatment at data cut-off date for an analysis, the subject is considered ongoing at the last dosing record.

#### *2.1.1.3 Study Day*

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

#### *2.1.1.4 Baseline*

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

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

For safety parameters (eg, ECGs or vital signs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline; if multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the average value should be considered as baseline while for the grade of laboratory tests the worst grade will be considered as baseline. For this study, safety laboratory testing is per local site laboratory.

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

#### *2.1.1.5 On-treatment Assessment/Event and Observation Periods*

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

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

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

***post-treatment period***: starting at Day 31 after last administration of study treatment in the single arm.

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

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

#### *2.1.1.6 Handling of Missing Values/Censoring*

Subjects who are of unknown clinical response or not assessed will be treated as nonresponders in the analyses of overall response rate (ORR).

Subjects who haven't experienced the specified event at the time of analysis will have time-to-event data (eg, progression-free survival, overall survival, etc.) censored at the time of last measurement prior to the data cut-off point used in the report.

## 2.2 Analysis Sets

### *2.2.1 Full Analysis Set*

The Full Analysis Set (FAS) includes all subjects who received at least one dose of infigratinib. Unless otherwise specified, all the analyses will be done separately for each cohort.

Unless otherwise specified, all the analyses will be conducted on FAS. All efficacy related analyses will be done separately for all subjects, subjects with baseline FGFR2 gene fusions or translocations and subjects with only other FGFR genomic alterations. In addition, for subjects with baseline FGFR2 gene fusions or translocations, the data will be summarized by treatment (formulation FMI I vs FMI III vs FMI IV). The analyses, including safety, disposition, demographic/baseline disease characteristics, study drug exposure and prior/concomitant/post therapy related analyses, will be done separately for all subjects, all subjects by FGFR status (FGFR2 gene fusion/translocation vs. only other FGFR genomic alterations) and all subjects by treatment.

Unless otherwise specified, the FAS will be used for all listings of raw data.

### *2.2.2 Interim Efficacy Analysis Set 1 for Cohort 1*

The Interim Efficacy Analysis Set 1 for Cohort 1 includes all subjects with planned extensive PK sample collection in Cohort 1 (regardless of whether extensive PK samples were actually collected) and all patients enrolled prior to Amendment 2. Unless otherwise specified, the Interim Efficacy Analysis Set 1 will be used as the primary efficacy analysis set for the first formal interim analysis for Cohort 1 after Amendment 3. Patients will be classified according to their baseline genetic status (FGFR2 gene fusions or translocations vs only other FGFR genetic alterations).

### *2.2.3 Interim Analysis Set 2 for Cohort 1*

The Interim Analysis Set 2 for Cohort 1 includes patients in Cohort 1 with FGFR2 gene fusions or translocations who have received at least one dose of infigratinib. Interim Analysis Set 2 for Cohort 1 will be used as the primary analysis set for the second formal interim analysis for Cohort 1 after Amendment 3.

### *2.2.4 Sensitivity Analysis Set for Cohort 1*

The Sensitivity Analysis Set for Cohort 1 includes patients with FGFR2 gene fusions or translocations who received infigratinib at the time of the first formal interim analysis and patients who have disease progression according to central imaging review or ended treatment by the cutoff date for the second formal interim analysis for Cohort 1 after Amendment 3. The cutoff date for the second formal interim analysis is planned so that all the patients with FGFR2 gene fusions or translocations who received infigratinib at the time of the first formal interim analysis have 10 months follow-up after their initial exposure to infigratinib. The Sensitivity Analysis Set for Cohort 1 will be used for supportive sensitivity analyses for the second formal interim analysis for Cohort 1. Some analyses, including summary of demographic, baseline characteristics and disposition, and some key efficacy and safety analyses, will be repeated on the Sensitivity Analysis Set.

### *2.2.5 Interim Analysis Set for Cohort 3*

The Interim Analysis Set for Cohort 3 will include the first 10 dosed subjects who have the potential to complete second scheduled post baseline scan.

### *2.2.6 Per-Protocol Set*

The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS who are compliant with requirements of the CSP in the following ways:

- Patient had an adequate tumor assessment at baseline
- Patient is evaluable for efficacy
- Patient had no CSR-reportable protocol deviations that may affect efficacy evaluation.

Subjects will be evaluable for efficacy if they have at least one post-baseline response assessed differently from 'unknown' or 'not assessed' as per RECIST v1.1. All CSR-reportable protocol deviations leading to exclusion from the PPS will be provided in a listing.

If more than 10% of FAS subjects were excluded from PPS, key efficacy analysis may be repeated on PPS.

### *2.2.7 Pharmacokinetic analysis set*

The Pharmacokinetic analysis set (PAS) includes all patients who (a) receive the planned treatment, (b) provide at least one evaluable PK concentration, and (c) do not vomit within 4 hours after the dosing of infigratinib.

Subjects will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples and whether the PK parameters can be reliably estimated based on the available blood samples. These patients will be identified at the time of the analyses.

### *2.2.8 Subgroups of interest*

The summaries of the efficacy variables may be repeated for the following subgroups:

- Lines of prior therapy (<=1 vs >1)
- Gender (male vs female)
- Age >=65 vs <65
- Region (North America vs Western Europe vs Asia)

Summaries for TEAEs will be repeated for the following subgroups:

- Gender (male vs female)
- Age group (>=65 vs <65)
- Region group (North America vs Western Europe vs Asia)
- BMI (<18.5 vs. >=18.5)
- Subjects who received strong CYP3A4 inhibitors vs moderate CYP3A4 inhibitors vs none (Section 5.10)

- Subjects who received strong CYP3A4 inducers vs moderate CYP3A4 inducers vs none (Section 5.10)

The list of strong CYP3A4 inhibitors and inducers is documented in Section 5.10.

## 2.3 Subject Disposition, Demographics and Other Baseline Characteristics

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

### *2.3.1 Subject disposition*

The following will be tabulated:

- Number (%) of patients treated;
- Number (%) of patients who are still on-treatment at the time of cut-off;
- Number (%) of patients who discontinued treatment and primary reasons for discontinuation.

A listing of disposition will be produced.

### *2.3.2 Demographics*

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data, eg, gender, age groups:<65 years vs ≥65 years, race, ECOG performance status, will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data, eg, age, weight, height will be summarized by descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum and maximum).

### *2.3.3 Medical History*

Summary of medical history will be provided by SOC and PT, using the Medical Dictionary for Regulatory Activities (MedDRA) (version 21.0 or later) terminology available at the time of reporting.

### *2.3.4 Prior Antineoplastic Therapy*

The number (%) of patients who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized. The summary will include only the prior antineoplastic therapy after or on the date of the initial diagnosis of cholangiocarcinoma.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen) and the total number of lines (excluding adjuvant or neoadjuvant regimens), setting at last treatment, best response at last treatment (defined to be the best response during the last treatment regimens recorded), best response during treatment with gemcitabine and cisplatin. For this analysis, gemcitabine and gemcitabine hydrochloride will be grouped to define prior treatment with gemcitabine. Prior

antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term. The summary of the efficacy endpoints, including response assessment, duration of response and time to progression, on the 1st line of gemcitabine base therapy will also be provided.

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.

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

### *2.3.5 Diagnosis and Extent of Cancer*

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histologic grade, stage at initial diagnosis, time (in months) since initial diagnosis of primary site to treatment start, time (in months) from initial diagnosis to first recurrence/relapse, time (in months) since most recent recurrence/relapse to treatment start, current extent of disease (metastatic sites).

## 2.4 Protocol Deviations

Unless otherwise specified, the FAS will be used for the protocol deviation summary tables and listing. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category as listed below:

- Subject enrolled and did not satisfy the entry criteria
- Subject developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Subject received the wrong treatment or incorrect dose
- Subject took a prohibited concomitant medication
- Major procedural or other GCP deviation that potentially affects patient safety or efficacy data interpretation

## 2.5 Treatments (Study Treatment, Concomitant Therapies, Compliance)

### *2.5.1 Study Treatment*

Unless otherwise specified, the full analysis set will be used for all summaries and listings of study treatment.

#### *2.5.1.1 Data Analysis*

Duration of exposure, actual cumulative dose, relative dose intensity (RDI) will be summarized in the full analysis set. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment.

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

#### *2.5.1.2 Duration of Exposure to Study Treatment*

*Duration of exposure (day) = (end date of infigratinib) – (start date of infigratinib) + 1,*

End date of infigratinib refers to the end date of last non-zero dose record with the exception for subjects who are still on treatment. For subjects who are still on treatment, the end date of infigratinib refers to the end date of last dose record.

Then,

*Duration of exposure (month) = Duration of exposure (day) / 30.4375*.

The duration of exposure to study treatment will be determined by the number of months exposed to infigratinib. Duration of exposure will be summarized using descriptive statistics.

Summary of duration of exposure of study drug will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries (ie, mean, standard deviation etc.) using appropriate units of time.

#### *2.5.1.3 Cumulative Dose*

Cumulative dose of study treatment is defined as the total dose given during the study treatment exposure and will be summarized.

The **planned cumulative dose** for study treatment refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

#### *2.5.1.4 Relative Dose Intensity*

Relative dose intensity (RDI) is defined as the ratio of actual cumulative dose to the planned cumulative dose. For example, a subject take study drug 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%.

RDI will be summarized. Summary of RDI will include categorical summaries based on the following categories: ≤0.5, >0.5 - ≤0.75, >0.75 - ≤0.9, >0.9 - ≤1.0 and >1.0.

#### *2.5.1.5 Dose Reductions, Interruptions*

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

Dose reductions will be summarized by the lowest non-zero dose level. Note that planned 1 week off in dosing schedule will not be collected or counted as dose interruption.

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

### *2.5.2 Prior, Concomitant and Post Therapies*

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Prior and Concomitant Medications eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Only on-treatment (treatment-emergent) concomitant medication (CM) will be summarized. On-treatment (treatment-emergent) concomitant medication refers to the concomitant medication taken on or after the first administration day of study drug and up to last study administration day of study drug +30 days. Some groups of concomitant medication may also be summary separately, for example, phosphate-binders.

The imputation of a concomitant medication start date and end date will follow the same conventions as for an AE start date if needed for analyses.

The post antineoplastic medication will be listed.

Prior, concomitant and post therapies may be listed as needed.

### *2.5.3 Compliance*

Compliance to the study treatment will be summarized in terms of the RDI or percentage of patients who took a predefined percentage of the number of prescribed. The predefined RDI categories are ≤0.5, >0.5 - ≤0.75, >0.75 - ≤0.9, >0.9 - ≤1.0 and >1.0. The number and proportion of patients falling in each category will be presented. Details are provided in Section 2.5.1.

## 2.6 Analysis of the primary objective

### *2.6.1 Variable*

For Cohort 1, the primary objective of the study is to assess anti-tumor activity of infigratinib using overall response rate assessed by central imaging review.

Best overall response (BOR) is the best overall response a subject ever achieves during the study prior to any subsequent anti-cancer therapy. Overall response rate (ORR) is defined as the proportion of patients with a best overall response of confirmed Complete Response (CR) or Partial Response (PR), as per RECIST version 1.1, among the corresponding analysis set.

ORR (central imaging assessment) is the primary efficacy endpoint, and its analysis consists of a Clopper-Pearson 95% CI accompanied by a characterization of time to response (TTR) and duration of response (DOR) to allow for a more complete characterization of the beneficial effect Infigratinib may have in the principal analysis population. The Brookmeyer-Crowley method will be used to construct the 95% CI for each of TTR and DOR.

### *2.6.2 Statistical Hypothesis, Model, and Method of Analysis*

For Cohort 1, the primary analysis of the primary endpoint (ORR assessed by central imaging review) should occur when all subjects in Cohort 1 have the potential to be followed for at least 10 months after their initial exposure to study treatment. The formal interim analysis for Cohort 1 will be conducted when all patients in the interim efficacy analysis set have been followed for at least 10 months after their initial exposure to the study treatment. Any confirmed PR or CR until the data cut-off date and any subsequent anti-cancer therapy will be considered as a responder for ORR, irrespective of when it occurred.

## 2.7 Analysis of Secondary Objective(s)

This section describes analyses of secondary objectives for Cohort 1. The same endpoints will be analyzed for Cohorts 2 and 3 as exploratory, so the approaches described in this section also apply to Cohort 2 and 3.

### *2.7.1 Secondary Efficacy Objectives*

**Overall Response Rate Per Investigator**

ORR per investigator is among the secondary endpoints. The estimated ORR will be presented with the corresponding 95% confidence interval based on exact binomial distribution using the corresponding analysis set.

**Overall Survival**

Overall Survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause. The survival time for subjects without documentation of death prior to the data cutoff will be censored at the last date the subject was known to be alive prior to the cutoff date. Survival time for subjects with no post-baseline survival information will be censored at the date of start of treatment.

OS will be analyzed using the Kaplan-Meier method. Survival rate at 4, 6, 8, 12, 18, 24 months (and every 6 months thereafter as reported in database) with median OS will be estimated along with 95% confidence intervals.

**Progression Free Survival**

Progression free survival (PFS) is defined as the date of the start of treatment to the date of the event defined as the first documented progression or death due to any cause, whichever is earlier. If subject has not had an event, progression-free-survival is censored at date of last valid tumor assessment or start of study treatment if there is no valid tumor assessment available. For subjects who had an event after two or more missed visits, the subject will be censored at the last adequate tumor assessment. The PFS analyses will be done based on central and local assessments separately. Kaplan-Meier analysis of PFS will be provided.

The primary PFS will be derived based on all the tumor assessments and death including any after a subsequent anti-cancer therapy. A sensitivity analysis will also be conducted on PFS excluding the tumor assessments and death after any subsequent anti-cancer therapies. If the event (the first progressive disease or death) is after a subsequent anti-cancer therapy, the PFS for the sensitivity analysis will be censored at the last valid tumor assessment prior to all subsequent anti-tumor therapies or first dose date if there is no valid tumor assessment prior to all subsequent anti-tumor therapies.

For Cohorts 2 and 3, the percentage of subjects who are progression-free at the second scheduled scan (approximately 16 weeks from treatment initiation) or later will be analyzed using 95% exact binomial confidence interval. Patients who do not have scans to show that they are progression-free at the second scheduled scan or later will be considered as not benefiting from the study treatment. Sensitivity analysis will be done by estimating PFS >16 weeks using K-M estimate.

**Best Overall Response and Disease Control Rate**

Overall lesion assessments will be listed by subject. BOR will be summarized for the rate of best overall response of progressive disease, stable disease, confirmed partial response (PR), and confirmed complete response (CR) separately; it will also summarized for the Disease Control Rate which are the proportion of subjects having respectively a best overall response of confirmed PR or CR, or stable disease. The estimates will be presented along with the corresponding 95% exact confidence interval. Best overall response will be provided for investigator assessment and central assessment as specified by cohort (Section 1.2). In addition, the concordance of best overall response based on central assessment and local assessment will be assessed.

Best tumor burden change (maximum tumor burden reduction from baseline or minimum tumor burden increase from baseline if tumor burden has never reduced prior to any anti-cancer therapy) will be presented graphically.

**Response Onset and Duration of Response**

Response onset will be estimated using Kaplan-Meier product limit method to analyze TTR based on ORR central imaging assessment. The Brookmeyer-Crowley method will be used to construct the 95% CI for TTR. DOR will be further summarized by length of exposure to

infigratinib using the following exposure cut-off lengths: at least 6 months, at least 9 months, at least 12 months.

Response onset and duration of response (DOR) will be summarized for confirmed responders only, based on local and central assessments separately. Response onset is defined as the time from the first study drug administration date to the initial response date. DOR is defined as the time from the initial response to the date of the event defined as the first documented progression or death due to any cause, whichever is earlier. The same event/censoring rule applied to PFS will be applied to DOR.

### *2.7.2 Safety Objectives*

The FAS will be used for summaries and listings of safety data except for the second formal interim analysis for Cohort 1 after amendment 3 where the Interim Analysis Set 2 for Cohort 1 will be used. In general, summaries will be provided only for the on-treatment safety assessments, which are the assessments occurring or taken during the on-treatment period.

#### *2.7.2.1 Adverse Events (AEs)*

##### 2.7.2.1.1 Data Handling

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

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

If CTCAE grading does not exist for an AE, Grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE Grade 5 (death) will not be used in this study. Death information will be collected on the “Death” eCRF pages.

##### 2.7.2.1.2 Data Analysis

**AE Summaries**

AE summaries will include all AEs occurring during on-treatment period, i.e. treatment emergent AEs. Treatment emergent AEs (TEAEs) include all AEs that started on or after the first administration day of study treatment and up to last study administration day of study treatment +30 days. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs, eg, AE relationship to study drug, AE outcome, etc. Treatment-emergent AEs will be flagged in the listings.

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

In TEAE summaries the primary system organ class will be presented alphabetically, and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in FAS. The following TEAE summaries will be produced by treatment and by FGFR2 fusion/translocation status:

- Overview of TEAEs and deaths (number and % of subjects who died from fatal TEAE, number and % of subjects with any TEAE, any treatment emergent serious AE, any TEAE leading to dose reductions/interruptions, TEAE leading to discontinuation of study treatment)
- All 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 with fatal outcome by SOC and PT and worst grade
- TEAE leading to study treatment discontinuation by SOC, PT and grade
- TEAE leading to dose interruption/adjustment by SOC, PT and grade
- TEAE leading to treatment discontinuation by SOC and PT and worst grade
- TEAE requiring additional medication or therapies by SOC and PT and worst grade
- All 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 by 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 treatment discontinuation by PT by descending order of frequency
- TEAE requiring additional medication or therapies by descending order of frequency

The following listings will be produced:

- All adverse events
- All serious adverse events

**Deaths**

Primary reason for on-treatment, post-treatment and all deaths will be summarized for the full analysis set. Treatment-emergent AE with fatal outcome will be summarized by SOC and PT. On-treatment death will also be summarized by SOC and PT.

All deaths will be listed and on-treatment death will be flagged.

**Adverse Events of Special Interest**

Adverse events of special interest (AESI) will be considered. 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) (Section 5.2 to Section 5.8). For each specified AESI, number and percentage of patients with at least one event within the AESI will be reported. The following AESI will be considered for this study:

- Calcium phosphate homeostasis, including the subcategories of hypercalcemia, hyperphosphatemia, and hypophosphatemia
- Eye disorder
- Central Serious Retinopathy/Retinal Pigment Epithelium Detachment (CSR/RPED)
- Cardiac disorder
- Acute pancreatitis
- Tissue calcification
- Pathological fracture
- Vascular calcification/mineralization

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. The current search strategy for each AESI is documented in Section 5.2.

**Minimum Critical Toxicities**

Minimal critical toxicities are toxicities that should always be explicitly considered during the planning for the development of every new medicinal product (Section 5.9). Analyses of these are based on FDA guidance as applicable (ie, Drug Induced Liver Injury using Hy's Law per FDA guidance).

Minimal critical toxicities to be analyzed under this statistical analysis plan include the following categories:

- Cardiac toxicity including QT prolongation and other ECG abnormalities
- Hepatotoxicity
- Nephrotoxicity
- Hematologic toxicity

Subject incidence of TEAEs indicative of potential cases of the toxicities will be summarized for each of the categories.

For hepatotoxicity, in addition, abnormalities in liver function tests will be summarized. Subject incidence of the following will be provided:

- 3×-, 5×-, 10×-, and 20× upper limit of normal (ULN) elevations of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT).
- Any elevations of bilirubin; elevated total bilirubin to ≥2×ULN.
- Any elevations of alkaline phosphatase (ALP) >1.5×ULN.
- Elevation of "ALT or AST" (>3×ULN) accompanied by elevated total bilirubin (>1.5×ULN, ≥2×ULN) and ALP <2×ULN.

In addition, a listing of potential Hy's Law cases identified will be provided. Potential hepatotoxicity is identified by the Hy's Law (FDA Guidance for Industry Drug Induced Liver Injury: Pre-marketing Clinical Evaluation, July 2009) as: ALT or AST >3.0×ULN; total bilirubin ≥2.0×ULN, ALP <2.0×ULN; and no other confounding factors including preexisting or acute liver disease.

For cardiac toxicity, ECG findings will also be summarized as specified in Section 2.7.3.3.

**Phosphate Binder Medication**

Number of subjects who have taken phosphate binder medication (Section 5.11) and the types of medication will be summarized by the formulation. Of these patients who have taken phosphate binder, number (percentage) of subjects who had a Grade 3/4 hypophosphatemia AE (including preferred terms hypophosphatemia and blood phosphorus decrease) will be summarized.

*2.7.2.2 Laboratory Data*

2.7.2.2.1 CTC Grading for Laboratory Parameters

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

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher for CTCAE parameters that are unidirectional. For CTCAE parameters that are bidirectional non-gradable values which are beyond the normal range will be left missing while Grade 0 will be assigned to the value within the normal range. Grade 5 is not applicable.

2.7.2.2.2 Imputation Rules

CTC grading for blood differentials is based on absolute values.

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

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

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

Corrected calcium can be derived using the reported total calcium value and albumin at the same assessment. The adjustment is done on calcium where albumin is less than 40 g/L and doesn't adjust when albumin ≥40 g/L because it can lead to underestimation. The formula for adjustment based on SI unit is:

When Albumin ≥40 g/L, then Corrected Calcium (mmol/L) = Calcium (mmol/l);

When non-missing Albumin <40 g/L, Corrected Calcium (mmol/L) = Calcium (mmol/L) + 0.02 × (40-Albumin(g/L))

In the formula above, SI unit mmol/L and g/L for Calcium and Albumin are used, respectively. The normal range of corrected calcium is same as the calcium's.

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

2.7.2.2.3 Data Analysis

The laboratory summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date. Laboratory parameters for hematology and blood chemistry will be summarized at baseline, each post-baseline visit (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.

For laboratory tests where grades are defined by CTCAE 4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE 4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE 4.03, the summary will be based on normal range:

- Worst post-baseline abnormal value (regardless of the baseline status). Each subject will be counted only once for the high/low category.
- Shift tables to compare baseline to worst on-treatment values using the low/normal/high/ (low and high)

For laboratory tests that are graded for both low and high directions, the shift tables and summary of post-baseline abnormal results will be done separately and labeled by direction.

As discussed in 'Minimum Critical Toxicities' in Section 2.7.2.1.2, incidence of potential drug-induced liver injury based AST, ALT, TBL, ALP will be presented and potential Hy's law cases will also be listed.

Table 4 provides an example of laboratory parameters for which CTCAE grades are defined, Table 5 provides an example of laboratory parameters for which shift tables were based upon the local lab normal range

**Table 4: Example of Laboratory Parameters for Which CTCAE Grades are Defined**

| Hematology and Coagulation | | Biochemistry | |
|---|---|---|---|
| White Blood Cells (WBC) | ↑ | Creatinine | ↑ |
| | ↓ | | |
| Hemoglobin | ↑ | Sodium | ↑ |
| | ↓ | | ↓ |
| Platelets counts | ↓ | Potassium | ↑ |
| | | | ↓ |
| Absolute Neutrophils | ↓ | Corrected Calcium | ↑ |
| | | | ↓ |
| Absolute Lymphocytes | ↑ | Magnesium | ↑ |
| | ↓ | | ↓ |
| APTT | ↑ | Albumin | ↓ |
| INR | ↑ | AST (SGOT) | ↑ |
| | | ALT (SGPT) | ↑ |
| | | Total Bilirubin | ↑ |
| | | Phosphate | ↓ |
| | | amylase | ↑ |
| | | lipase | ↑ |
| | | Alkaline phosphatase | ↑ |
| | | Total Cholesterol | ↑ |
| | | Triglycerides | ↑ |
| | | Urate | ↑ |

↑ Indicates that CTC grade increases as the parameter increases.
↓ Indicates that CTC grade increases as the parameter decreases.

**Table 5: Examples of Laboratory Parameters (Without CTCAE Grades) for Which Lab Reference Ranges Are Defined**

| Hematology and Coagulation | Biochemistry |
|---|---|
| Prothrombin time (PT) | Blood urea nitrogen (BUN) |
| Hematocrit | Urea |
| Absolute Basophils, | Total protein |
| Absolute Eosinophils | Direct Bilirubin |
| Absolute Monocytes | Indirect Bilirubin |
| | Chloride |
| Red Blood Cells (RBC) | |

### *2.7.3 Other Safety Data*

The FAS will be used for summaries and listings of other safety data discussed in this section except for the second formal interim analysis for Cohort 1 after Amendment 3 where the Interim

Analysis Set 2 for Cohort 1 will be used. In general, summaries will be provided only for the on-treatment safety assessments, which are the assessments occurring or taken during the on-treatment period.

#### *2.7.3.1 Ophthalmologic Assessment*

Both visual acuity score (logMAR) and tonometry will be summarized at baseline, each post-baseline visit (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.

#### *2.7.3.2 Left Ventricular Ejection Fraction*

Left ventricular ejection fraction (LVEF) will be summarized for baseline, each post-baseline visit (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%

#### *2.7.3.3 ECG and Cardiac Imaging Data*

The ECG analysis will be performed on all subjects who have received at least one dose of infigratinib with the baseline and at least one on-treatment post-baseline ECG assessment.

The average of the ECG parameters at each assessment should be used in the analyses. 12-lead ECGs including PR, QRS, QT, QTcF, QTcB, and HR intervals will be obtained central/local for each subject during the study. ECG data will be read and interpreted centrally. 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, each post-baseline visit (based on the nominal visit as collected from eCRF), the maximum and minimum observed post-baseline values, and last observed value, along with the change from baseline. For the maximum/minimum/last observed value, both scheduled and unscheduled assessments will be considered.

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

- QT
  - New value of >500 ms
- QT, 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 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.

In addition to the ECG analysis in CSR, a separate report on cardiac safety evaluation including QTc/PK modeling will be provided, based on a separate cardiac safety analysis plan.

#### *2.7.3.4 Vital Signs and ECOG Performance Status*

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

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

Vital signs (except height) collected during on-treatment will also be summarized using the same approach as for ECOG. The number and percentage of subjects with notable vital sign values (high/low) will be presented.

**Table 6: Criteria for Notable Vital Sign Values**

| Vital sign (unit) | Notable high value | Notable low value |
|---|---|---|
| Systolic blood pressure (mmHg) | ≥180 and increase from baseline of ≥20 | ≤90 and decrease from baseline of ≥20 |
| Diastolic blood pressure (mmHg) | ≥105 and increase from baseline of ≥15 | ≤50 and decrease from baseline of ≥15 |
| Pulse rate (bpm) | ≥100 and increase from baseline of >25% | ≤50 and decrease from baseline of >25% |
| Body temperature (°C) | ≥39.1 | -- |

#### *2.7.3.5 Supportive Analyses for Secondary Objectives*

Not applicable.

#### *2.7.3.6 Tolerability*

Tolerability of study drug will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by subject and summarized. Cumulative dose, dose intensity and relative dose intensity of infigratinib will be listed by subject and summarized. Categories for relative dose intensity of infigratinib will be specified as ≤0.5, >0.5 - ≤0.75, >0.75 - ≤0.9, >0.9 - ≤1.0, and >1.0. The number and proportion of subjects within each category will be presented.

### *2.7.4 Pharmacokinetics*

Subjects treated with FMI I and some subjects treated with FMI III (sparse PK group) will have limited PK collected as indicated in Table 10 of CSP Amendment 5. For these subjects, only trough and 2-hr or 4-hr plasma concentration data will be collected. No PK parameters can be calculated for these subjects, but the concentration data may be used in the population PK modeling.

A secondary objective of this study is to characterize the single and multiple doses PK of infigratinib FMI III and FMI IV formulations. Data as per Table 11 of CSP Amendment 5 will be available for about 20 subjects treated with FMI III and for all subjects enrolled in either Cohort 2 or Cohort 3 and treated with FMI IV. For these subjects, PK parameters as listed in Table 7, may be determined from PK profiles after the first dose on Day 1 of Cycle 1 and Day 15

of Cycle 1 after repeated daily dosing using non-compartmental method(s) of WinNonlin (Pharsight, Mountain View, CA).

The sections below on the PK analysis are intended to provide general principle for the PK analysis. Additional details of the analysis approaches will be provided in a separate PK analysis plan.

**Table 7: Non-compartmental Pharmacokinetic Parameters**

| Term | Definition |
|---|---|
| $C_{max}$ | Maximum observed plasma concentration after drug administration [mass × volume$^{-1}$] |
| $C_{trough}$ | Measured concentration at the end of a dosing interval (taken directly before next administration) [mass × volume$^{-1}$] |
| $T_{max}$ | Time to reach $C_{max}$ [time] |
| $AUC_{0-24}$ | Area under the concentration-time curve from 0 to 24 hours [mass × time × volume$^{-1}$] |
| $T_{1/2}$ | Elimination half-life associated with the terminal slope (lambda_z) of a semi-logarithmic concentration-time curve [time] |
| $AUC_{inf}$ | Area under the concentration-time curve from 0 to infinity [mass × time × volume$^{-1}$] |
| CL/F | Apparent clearance [dose/AUC] |
| Vz/F | Apparent volume of distribution [dose/AUC × lambda_z] |
| $R_{acc}$ | Accumulation ratio calculated as $AUC_{0-24}$ of C1D15/$AUC_{0-24}$ of C1D1 and $C_{max}$ of C1D15/ $C_{max}$ of C1D1 |

#### *2.7.4.1 Data Handling Principles*

Only PK blood samples with the date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Missing concentration values will be reported as is in data listings. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing. Below the limit of quantitation (BLQ) values will be displayed in the listings as is. BLQ values will be treated as zero for the calculation of the geometric means and geometric CV%.

At the time of analysis, concentration data from subjects may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific time points might be removed from the analysis set if technical issues with the sample are reported (eg, sampling issues, missing information). These data points will be identified at the time of analysis

#### *2.7.4.2 Data Analysis Principles*

Exploratory PK analysis may be conducted based on preliminary data prior to data base lock, and nominal time and dose information may be used.

PK data generated from this study may be used in conjunction with PK data from other clinical studies for population PK and PK/PD assessment. These assessments will be reported separately. If possible, exploratory comparisons will be made to historical pharmacokinetic data. Available PK data from this study may be modeled using a population pharmacokinetic data analysis approach in order to characterize the population pharmacokinetics of infigratinib. Any population PK data generated will be reported separate from the CSR.

All analyses will refer to infigratinib and its metabolites. Infigratinib and its metabolites concentration vs time data will be reported.

Analysis will be done separately for the three formulations. In addition, analyses that require derived PK parameters will be applicable to subjects treated with FMI III and FMI IV who have provided PK parameters based on extensive PK sampling as indicated in Table 11 of CSP Amendment 5.

#### *2.7.4.3 Analysis Sets*

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

#### *2.7.4.4 Basic Tables, Figures, and Listings*

The PK concentration and PK parameters (when available for subjects treated with FMI III or FMI IV), will be summarized and listed using relevant statistics by treatment, and study day. Descriptive statistics (mean, SD, CV%, geometric mean, geometric CV%, median, and range) will be presented. Median, minimum and maximum will be calculated based on collected samples. When a geometric mean is presented, it will be stated as such. Only median values and ranges will be presented for $T_{max}$.

Graphical plots of individual and mean plasma concentration-time data will be generated for infigratinib and its metabolites. This graphical presentation will be applicable to subjects who are treated with FMI III and have PK profile collected as per Table 11 of CSP Amendment 5. Further graphical exploratory analysis will be carried out if deemed appropriate.

Median, minimum and maximum will be calculated based on collected samples. All analyses will refer to infigratinib and its metabolites. Infigratinib and its metabolites concentration vs time data will be reported. Exploratory PK analysis may be conducted based on preliminary data prior to data base lock and nominal time and dose information may be used.

## 2.8 Exploratory Analyses

The exploratory analyses described below will be conducted if there are sufficient data available.

### *2.8.1 Biomarkers*

Sequencing analyses of cell-free DNA (cfDNA) isolated from the plasma of a subset of subjects who have progressed through treatment with Infigratinib are performed in order to detect genetic alterations from baseline.

#### *2.8.1.1 Outline of the Data Analysis*

Since the clinical trial was not designed to address specific hypotheses related to subject pre-selection or resistance markers, the analysis of this data should be viewed as exploratory. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is planned.

If the number of samples is inadequate to perform a rigorous data analysis, then the available data will only be listed. Additional analyses that may be performed after the completion of the end-of-study clinical study report will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of subject pre-selection or PD markers generated from samples collected during the study but analyzed after the database lock and completion of the clinical study report. Any additional data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

#### *2.8.1.2 Data Handling Principles*

All measurements below their respective LLOQs or missing data will be labeled as such in the concentration data listings. Measurements below the LLOQ will be treated as zero in summary statistics. Change from baseline analyses will only be performed on subjects with measurable samples and pre- and post-treatment time points.

#### *2.8.1.3 Data Analysis Principles*

##### 2.8.1.3.1 Analysis Sets

The FAS will be used for all analyses unless otherwise specified. The number of subjects with measurable samples will be identified in the summaries and relevant proportions will be calculated against this number of subjects.

##### 2.8.1.3.2 Basic Tables, Figures, and Listings

Change from baseline for markers measured pre and post baseline to assess the effect on FGFR pathway will be listed by subject and may be summarized by means of descriptive statistics.

Individual CA19-9 serum levels (or change from baseline) will be listed as well as presented as line plots over time. If enough data is available, statistical analysis will be performed in order to assess the relationship between anti-tumor activity (BOR and OS) and CA19-9 levels (or change

from baseline). Best percent change in the sum of longest tumor diameters and the percent change in CA19-9 concentration from baseline will be plotted together in a bar graph.

Subject's FGFR2 gene fusion status in DNA from non-tumor tissue (cell free DNA data) will be listed and compared to the FGFR2 gene fusion status in tumor tissue at baseline; a contingency table will be presented. Genetic alterations detected in cell free tumor DNA will be summarized and presented graphically for subjects with both baseline and post-baseline samples. If there is enough data, change from baseline expression levels will be correlated with efficacy data. Further exploratory analyses will be performed if feasible.

## 2.9 Interim Analysis

Safety and efficacy data will be continuously monitored by QED Therapeutics in conjunction with the investigators for decision-making purposes.

For Cohort 1, one analysis was performed before Amendment 2 based on the 61 patients enrolled in the study (30 Jun 2016). Protocol amendment 2 restricted enrollment to patients with FGFR2 fusions or translocations, and the formulation was changed from FMI I to FMI III.

After 20 subjects had been treated with FMI III (for at least one cycle) based on Amendment 2, a comprehensive review of all relevant data such as PK, safety, dose interruptions/reductions, and available efficacy was performed. PK, safety, and tolerability data from the first 20 subjects treated with FMI III up to the end of cycle 1 of treatment were assessed and compared with the historical data from subjects treated with FMI I. Upon review of the data, it was decided to continue dosing all subsequent patients treated with FMI III at 125 mg on a 3 weeks on, 1 week off schedule.

In addition, two formal interim analyses for Cohort 1 are planned after Amendment 3:

- The first formal interim analysis for Cohort 1 was conducted when all patients in the Interim Efficacy Analysis Set 1 have been followed for at least 10 months after their initial exposure to the study treatment. This interim analysis will be done using only patients in Cohort 1. Efficacy analysis for this interim analysis will be based on the Interim Efficacy Analysis Set 1 and some key efficacy analyses may be repeated in the FAS. All the other analyses will be conducted on FAS unless otherwise specified.

- The second will be conducted when all the patients who received infigratinib at the time of the first formal interim analysis have at least 10 months follow-up after their initial exposure to infigratinib.

Additionally, for Cohorts 2 and 3, review of data will be performed after a total of 15 patients in either Cohort 2 or 3 have been treated with FMI IV for at least one cycle. A formal interim analysis will be conducted for Cohort 3 when the first dosed 10 patients in Cohort 3 have the potential to complete the second scheduled scan. This interim analysis will only include data from Cohort 3. This is to determine if an additional 10 patients will be added to Cohort 3.

# 3 SAMPLE SIZE CALCULATION

## 3.1 Cohort 1

At the time of the first formal interim analysis after amendment 3, the interim efficacy analysis set 1 will include 72 patients with FGFR2 gene fusions or translocations. The half-width of the exact 95% confidence interval for ORR will not exceed 12%.

With at least 106 subjects with FGFR2 gene fusions or translocation will result in the exact 95% confidence interval half-width of ORR less than 10%.

## 3.2 Cohort 2 and Cohort 3

In Cohorts 2 and 3, patients who are progression-free at the second scheduled post-baseline scan (approximately 16 weeks from treatment initiation) or later will be considered to be benefiting from study treatment. If the lower bound of the patients who are progression-free at the second scheduled post-baseline scan (approximately 16 weeks) or later excludes 20%, the treatment will be considered as benefiting the patients.

For Cohort 2, the percentage of patients who are progression-free at the second scheduled post-baseline scan (approximately 16 weeks) or later will be estimated with 95% exact confidence interval. There will be approximately 20 patients in total. A sample size of 20 will result in the exact 95% confidence interval half width of less than 23%. Patients who withdraw from the study for any reason before the second scheduled scan will be considered as not benefiting from study treatment. Sensitivity analysis will be conducted using the K-M method to estimate PFS >16 weeks.

Table 8 provides some examples of CIs corresponding to observed numbers of patients considered to have benefited from treatment. For example, if 9 of 20 patients are progression-free at the second scheduled post-baseline scan or later, then the lower bound of the 95% exact confidence interval (CI) will exclude 20%.

In Cohort 3, the same definition of benefit rate as for Cohort 2 (the percentage of patients who are progression-free at the second scheduled post-baseline scan [approximately 16 weeks] or later) will be applied. The benefit rate will be estimated with 95% exact confidence interval. The planned enrollment for Cohort 3 is a maximum of 20 patients. With 20 patients, the exact 95% confidence interval half width is <23%. One interim analysis is planned when 10 patients have been dosed and have the potential to be followed up for response for at least 2 scheduled post-baseline scans. If at the interim analysis, ≥4 patients are progression-free at the second scheduled post-baseline scan (after approximately 16 weeks) or later, the cohort will continue to enroll the additional 10 patients; otherwise, enrollment will stop at 10 patients. If ≤20% patients are benefiting from the study treatment, there is <12.1% chance that the decision after the interim analysis will lead to continuing enrollment.

The percentage of patients considered to have benefited from treatment will be estimated with 95% exact binomial CI. If all 20 patients are enrolled, the exact 95% CI half width will not exceed 23%. Table 8 provides some examples of CIs corresponding to observed numbers of

subjects considered to have benefited from treatment. At the final analysis, if 9 of 20 subjects who are progression-free at the second scheduled post-baseline scan or later, the lower bound of the 95% exact CI will exclude 20%.

**Table 8: 95% CI Examples Corresponding to Observed Numbers of Subjects Considered to Have Benefited From Treatment (Cohorts 2 and 3)**

| Number of subjects considered to have benefited from treatment | 95% Exact CI |
|---|---|
| 4 | (0.057, 0.437) |
| 8 | (0.191, 0.640) |
| 9 | (0.231, 0.685) |
| 10 | (0.272, 0.728) |
| 12 | (0.361, 0.809) |

CI=confidence interval

# 4 CHANGE TO PROTOCOL SPECIFIED ANALYSES

None.

# 5 APPENDIX

## 5.1 Imputation Rules

### *5.1.1 AE, CM, and Safety Assessment Date Imputation*

**Table 9: Imputation of Start Dates (AE, CM)**

| 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<br>○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.<br>○ Else set start date = study treatment start date.<br>• If available month and year > month and year of study treatment start date then 01MONYYYY<br>• If available month and year < month year of study treatment start date then 01MONYYYY |

**Table 10: Imputation of End Dates (AE, CM)**

| Subject EOT (Y/N) | Missing Element | Rule (*= min (last treatment date plus 30 days, death date, cut-off date, withdrawal of consent date)) |
|---|---|---|
| N | day, month, and year | • Data cutoff date |
| Y | day, month, and year | • Completely missing end dates will be imputed by the end date of the on-treatment period* |
| | day, month | • If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period * |
| | day | • If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period* |

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

There should be no cases where AE or CM end dates are partial missing (year is available but month or day or both are missing) if a subject has not ended study treatment (EOT). The above imputations are only used for the calculation of time to and duration of AEs and concomitant medications.

### *5.1.2 Death Date Imputation*

If day is missing, then impute to the 1st of the month unless last known to be alive date is greater than the 1st of the month, in that case, set the death date to the last known to be alive date.

## 5.2 Table of Adverse Events of Special Interest, Search Strategies, and Rationales for Sponsor-Defined Search Strategies

| Adverse Event of Special Interest | Search Strategy |
|---|---|
| Calcium-phosphate homeostasis[1]<br>• Hypercalcaemia<br>• Hyperphosphataemia<br>• Hypophosphataemia | Sponsor-defined grouped PTs |
| Eye disorder[2] | Sponsored-defined PTs in SOC Eye disorder:<br>CSR/RPED<br>Eye disorder other than RPED |
| Central serous retinopathy/retinal pigment epithelium detachment (CSR/RPED)[3] | Subset of PTs from SOC Eye disorders |
| Cardiac disorder* | Cardiac failure SMQ [narrow, broad]<br>Myocardial infarction SMQ [narrow, broad]<br>Other ischaemic heart disease SMQ [narrow, broad]<br>Cardiac arrhythmia terms, nonspecific SMQ [narrow]<br>Bradyarrhythmia terms, nonspecific SMQ [narrow]<br>Tachyarrhythmia terms, nonspecific SMQ [narrow]<br>Arrhythmia related investigations, signs and symptoms SMQ [narrow, broad] |
| Acute pancreatitis | Acute pancreatitis SMQ [narrow, broad] |
| Pathological fracture[4] | Sponsor-defined PTs |
| Tissue calcification[5] | Sponsor-defined PTs |
| Vascular/intravascular mineralization[6] | Sponsor-defined Grouped PTs |

* Note: SMQs relating to Torsade de Pointes / QT prolongation and cardiac arrhythmias are part of Minimum Critical Toxicity: Cardiac toxicity Rationales for Sponsor-defined grouped terms:

1 Sponsor-defined PTs capture the medical concept of hypercalcaemia, hyperphosphataemia, and hypophosphataemia. No SMQs available for these terms.

2 Sponsor-defined PTs in the SOC Eye Disorders, including 9 PTs used to characterize CSR/RPED, broadly capture eye related events. No SMQ available for this medical concept.

3 A narrow subset of PTs from SOC Eye Disorder (as selected by an ophthalmologist) are grouped to capture the medical concept of RPED. No SMQ available for this medical concept.

4 Sponsor-defined PTs include PTs with 'fracture', which capture the broad medical concept of fractures, recognizing that any fracture could be pathological in nature for the population under study. No SMQ available for this medical concept.

5 Sponsor-defined PTs include PTs with 'calcification' and 'calcinosis' which capture the broad medical concept of tissue calcification. No SMQ available for this medical concept.

6 Sponsor-defined PTs include PTs with targeted root words (athero, arterio, and sclerosis) and words (arterial, artery, calcification, insufficiency, mineralization, peripheral, and venous) with medical judgement to refine on terms which capture the broad medical concept of vascular calcification/mineralization. No SMQ available for this medical concept.

## 5.3 AESI: Calcium-Phosphate Homeostasis – Hypercalcaemia, Hyperphosphataemia, and Hypophosphataemia

| AESI | Sponsor-Defined Grouped PTs |
|---|---|
| Hypercalcaemia | Adjusted calcium increased<br>Blood calcium abnormal<br>Blood calcium increased<br>Calcium ionised abnormal<br>Calcium ionised increased<br>Calcium phosphate product increased<br>Hypercalcaemia |
| Hyperphosphataemia | Blood phosphorus abnormal<br>Blood phosphorus increased<br>Hyperphosphataemia |
| Hypophosphataemia | Blood phosphorus decreased<br>Hypophosphataemia |

## 5.4 AESI: Eye Disorder of Central Serous Retinopathy/Retinal Pigment Epithelium Detachment

AESI of Eye disorder is characterized by PTs from SOC Eye disorders. CSR/RPED terms are listed below and remaining eye disorders (excluding PTs used to characterize CSR/RPED) are listed in Section 5.8.

| AESI | Sponsor-Defined Grouped PTs |
|---|---|
| Central serous retinopathy/retinal pigment epithelium detachment (CSR/RPED) | Chorioretinopathy<br>Detachment of macular retinal pigment epithelium<br>Detachment of retinal pigment epithelium<br>Macular detachment<br>Retinal detachment<br>Serous retinal detachment<br>Subretinal fluid<br>MEK inhibitor-associated serous retinopathy<br>Retinopathy |

## 5.5 AESI: Pathological Fracture

| Sponsor-Defined Grouped PTs | Sponsor-Defined Grouped PTs | Sponsor-Defined Grouped PTs |
|---|---|---|
| Fracture | Fracture nonunion | Osteochondral fracture |
| Acetabulum fracture | Fracture of clavicle due to birth trauma | Osteophyte fracture |
| Ankle fracture | Fracture of penis | Osteoporotic fracture |
| Atypical femur fracture | Fracture pain | Patella fracture |
| Atypical fracture | Fracture reduction | Pathological fracture |
| Avulsion fracture | Fracture treatment | Pelvic fracture |
| Cervical vertebral fracture | Fractured coccyx | Periprosthetic fracture |
| Chance fracture | Fractured ischium | Pseudofracture |
| Clavicle fracture | Fractured maxilla elevation | Pubis fracture |
| Closed fracture manipulation | Fractured sacrum | Radius fracture |
| Comminuted fracture | Fractured skull depressed | Rib fracture |
| Complicated fracture | Fractured zygomatic arch elevation | Sacroiliac fracture |
| Compression fracture | Greenstick fracture | Scapula fracture |
| Costal cartilage fracture | Hand fracture | Skull fracture |
| Craniofacial fracture | Hip fracture | Skull fractured base |
| Elevation skull fracture | Humerus fracture | Spinal compression fracture |
| Epiphyseal fracture | Ilium fracture | Spinal fracture |
| External fixation of fracture | Impacted fracture | Spinal fusion fracture |
| Facial bones fracture | Internal fixation of fracture | Sternal fracture |
| Femoral neck fracture | Jaw fracture | Stress fracture |
| Femur fracture | Limb fracture | Subchondral insufficiency fracture |
| Fibula fracture | Lisfranc fracture | Surgical fixation of rib fracture |
| Foot fracture | Loss of anatomical alignment after fracture reduction | Thoracic vertebral fracture |
| Forearm fracture | Lower limb fracture | Tibia fracture |
| Fracture blisters | Lumbar vertebral fracture | Tooth fracture |
| Fracture debridement | Metaphyseal corner fracture | Torus fracture |
| Fracture delayed union | Multiple fractures | Traumatic fracture |
| Fracture displacement | Open fracture | Ulna fracture |
| Fracture infection | Open reduction of fracture | Upper limb fracture |
| Fracture malunion | Open reduction of spinal fracture | Wrist fracture |

## 5.6 AESI: Tissue Calcification

| Sponsor-Defined Grouped PTs | Sponsor-Defined Grouped PTs | Sponsor-Defined Grouped PTs |
|---|---|---|
| Administration site calcification | Infusion site calcification | Splenic calcification |
| Adrenal calcification | Injection site calcification | Tendon calcification |
| Application site calcification | Intervertebral disc calcification | Thyroid calcification |
| Articular calcification | Intestinal calcification | Tracheal calcification |
| Bladder wall calcification | Ligament calcification | Vaccination site calcification |
| Bone decalcification | Lymph node calcification | Calcinosis |
| Breast calcifications | Medical device site calcification | Chondrocalcinosis |
| Bursa calcification | Myocardial calcification | Chondrocalcinosis pyrophosphate |
| Calcification metastatic | Ovarian calcification | Gastric mucosal calcinosis |
| Calcification of muscle | Pancreatic calcification | Nephrocalcinosis |
| Catheter site calcification | Pericardial calcification | |
| Cerebral calcification | Pleural calcification | |
| Cutaneous calcification | Postoperative heterotopic calcification | |
| Dystrophic calcification | Primary familial brain calcification | |
| Hepatic calcification | Prostatic calcification | |
| Implant site calcification | Pulmonary calcification | |

## 5.7 AESI: Vascular/intravascular Mineralization

| Sponsor-Defined Grouped PTs | Sponsor-Defined Grouped PTs | Sponsor-Defined Grouped PTs |
|---|---|---|
| Acute vascular insufficiency of intestine | Coeliac artery occlusion | Peripheral artery restenosis |
| Aortic arteriosclerosis | Coeliac artery stenosis | Peripheral artery stenosis |
| Aortic valve calcification | Coronary artery disease | Peripheral vascular disorder |
| Arterial insufficiency | Coronary artery insufficiency | Precerebral arteriosclerosis |
| Arterial insufficiency coronary | Coronary artery occlusion | Precerebral artery occlusion |
| Arterial insufficiency peripheral | Coronary artery reocclusion | Pulmonary artery occlusion |
| Arteriosclerosis | Coronary artery restenosis | Pulmonary artery stenosis |
| Arteriosclerosis coronary artery | Coronary artery stenosis | Pulmonary valve calcification |
| Arteriosclerotic retinopathy | Heart valve calcification | Renal arteriosclerosis |
| Atherosclerotic plaque rupture | Hepatic artery flow decreased | Renal artery arteriosclerosis |
| Basilar artery occlusion | Hepatic artery occlusion | Renal artery occlusion |
| Basilar artery stenosis | Hepatic artery stenosis | Renal artery restenosis |
| Basilar insufficiency | Iliac artery disease | Renal artery stenosis |
| Brachiocephalic arteriosclerosis | Iliac artery occlusion | Retinal artery occlusion |
| Brachiocephalic artery occlusion | Inner ear vascular insufficiency | Retinal artery stenosis |
| Brachiocephalic artery stenosis | Insufficiency cerebrovascular | Splenic artery stenosis |
| Carotid arteriosclerosis | Insufficiency coronary artery | Subclavian artery occlusion |
| Carotid artery insufficiency | Intraoperative cerebral artery occlusion | Subclavian artery stenosis |
| Carotid artery occlusion | Mesenteric arteriosclerosis | Tricuspid valve calcification |
| Carotid artery restenosis | Mesenteric artery stenosis | Unspecified vascular insufficiency of intestine |
| Carotid artery stenosis | Mesenteric vascular insufficiency | Vascular calcification |
| Cerebellar artery occlusion | Microvascular coronary artery disease | Vascular insufficiency |
| Cerebral arteriosclerosis | Mitral valve calcification | Vascular insufficiency of intestine |
| Cerebral artery occlusion | Penile artery occlusion | Vascular insufficiency of intestine, unspecified |
| Cerebral artery restenosis | Peripheral arterial occlusive disease | Vertebral artery occlusion |
| Cerebral artery stenosis | Peripheral arterial reocclusion | Vertebral artery stenosis |
| Cerebrovascular insufficiency | Peripheral artery occlusion | Vertebrobasilar insufficiency |
| Chronic vascular insufficiency of intestine | | |

## 5.8 AESI: Eye Disorder: SOC Eye Disorders (Excluding 9 PTs Used to Characterize CSR/RPED)

There are two subcategories in the eye disorder AESI summary table, one for CSR/RPED which included 9 PTs described in Section 5.4, the other is Eye Disorder SOC Other than CSR/RPED which included the remaining eye disorders not included in CSR/RPED section and are described in this section.

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Abnormal sensation in eye | Exfoliation syndrome | Ocular ischaemic syndrome |
| Abscess of eyelid | Exophthalmos | Ocular lymphoma |
| Acanthamoeba keratitis | Exophthalmos congenital | Ocular myasthenia |
| Accommodation disorder | Exposure keratitis | Ocular neoplasm |
| Acquired corneal dystrophy | Extraocular muscle disorder | Ocular pemphigoid |
| Acquired epiblepharon | Extraocular muscle paresis | Ocular procedural complication |
| Acquired lenticonus | Extraocular retinoblastoma | Ocular retrobulbar haemorrhage |
| Acquired pigmented retinopathy | Exudative retinopathy | Ocular rosacea |
| Acute haemorrhagic conjunctivitis | Eye abscess | Ocular sarcoidosis |
| Acute macular outer retinopathy | Eye allergy | Ocular surface disease |
| Acute myopia | Eye anterior chamber congenital anomaly | Ocular toxicity |
| Acute zonal occult outer retinopathy | Eye burns | Ocular vascular disorder |
| Adenoviral conjunctivitis | Eye colour change | Ocular vasculitis |
| Age-related macular degeneration | Eye complication associated with device | Oculocerebrorenal syndrome |
| AIDS retinopathy | Eye contusion | Oculodentodigital dysplasia |
| Allergic keratitis | Eye degenerative disorder | Oculoglandular syndrome |
| Alstroem syndrome | Eye discharge | Oculogyric crisis |
| Altered visual depth perception | Eye disorder | Oculomucocutaneous syndrome |
| Amaurosis | Eye haemangioma | Oculopharyngeal dystrophy |
| Amaurosis fugax | Eye haematoma | Oculorespiratory syndrome |
| Amblyopia | Eye haemorrhage | Onchocerciasis |
| Amblyopia alcohol | Eye infection | Open angle glaucoma |
| Amblyopia congenital | Eye infection bacterial | Open globe injury |
| Amblyopia strabismic | Eye infection chlamydial | Ophthalmia neonatorum |
| Amblyopia tobacco | Eye infection fungal | Ophthalmia nodosa |
| Angle closure glaucoma | Eye infection gonococcal | Ophthalmic herpes simplex |
| Aniridia | Eye infection helminthic | Ophthalmic herpes zoster |
| Aniseikonia | Eye infection intraocular | Ophthalmic vein thrombosis |
| Anisometropia | Eye infection staphylococcal | Ophthalmoplegia |
| Anomaly of orbit, congenital | Eye infection syphilitic | Ophthalmoplegic migraine |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Anophthalmos | Eye infection toxoplasmal | Opitz-G/BBB syndrome |
| Anterior capsule contraction | Eye infection viral | Opsoclonus myoclonus |
| Anterior chamber angle neovascularisation | Eye inflammation | Optic atrophy |
| Anterior chamber cell | Eye injury | Optic disc disorder |
| Anterior chamber cleavage syndrome | Eye irritation | Optic disc drusen |
| Anterior chamber collapse | Eye laser scar | Optic disc haemorrhage |
| Anterior chamber crystallisation | Eye luxation | Optic disc hyperaemia |
| Anterior chamber degeneration | Eye movement disorder | Optic disc pit |
| Anterior chamber disorder | Eye muscle entrapment | Optic disc telangiectasia |
| Anterior chamber fibrin | Eye naevus | Optic disc vascular disorder |
| Anterior chamber flare | Eye oedema | Optic discs blurred |
| Anterior chamber inflammation | Eye opacity | Optic glioma |
| Anterior chamber opacity | Eye pain | Optic ischaemic neuropathy |
| Anterior chamber pigmentation | Eye paraesthesia | Optic nerve compression |
| Anterior segment ischaemia | Eye pruritus | Optic nerve cupping |
| Antimetropia | Eye swelling | Optic nerve disorder |
| Aphakia | Eye symptom | Optic nerve hypoplasia |
| Aphakia congenital | Eye ulcer | Optic nerve infarction |
| Aqueous fibrin | Eyeball avulsion | Optic nerve injury |
| Aqueous humour leakage | Eyelash changes | Optic nerve neoplasm |
| Arcus lipoides | Eyelash discolouration | Optic nerve sheath haemorrhage |
| Argyll-Robertson pupils | Eyelash hyperpigmentation | Optic neuritis |
| Arteriosclerotic retinopathy | Eyelash hypopigmentation | Optic neuritis meningococcal |
| Asthenopia | Eyelash injury | Optic neuropathy |
| Astigmatism | Eyelash thickening | Optic pathway injury |
| Atopic cataract | Eyelid bleeding | Orbit atrophy |
| Atopic keratoconjunctivitis | Eyelid boil | Orbital apex syndrome |
| Atrophy of globe | Eyelid contusion | Orbital compartment syndrome |
| Autoimmune retinopathy | Eyelid cyst | Orbital cyst |
| Autoimmune uveitis | Eyelid degenerative disorder | Orbital granuloma |
| Bacterial blepharitis | Eyelid disorder | Orbital infection |
| Bacterial dacryocystitis | Eyelid erosion | Orbital myositis |
| Bacterial iritis | Eyelid exfoliation | Orbital oedema |
| Balint's syndrome | Eyelid folliculitis | Oscillopsia |
| Basal cell naevus syndrome | Eyelid function disorder | Osteoporosis-pseudoglioma syndrome |
| Basedow's disease | Eyelid haemangioma | Ota's naevus |
| Behcet's syndrome | Eyelid haematoma | Overwear syndrome |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Bell's phenomenon | Eyelid infection | Panophthalmitis |
| Benign neoplasm of choroid | Eyelid injury | Papilloedema |
| Benign neoplasm of conjunctiva | Eyelid irritation | Papilloma conjunctival |
| Benign neoplasm of cornea | Eyelid margin crusting | Papillophlebitis |
| Benign neoplasm of eye | Eyelid myoclonus | Paralytic lagophthalmos |
| Benign neoplasm of eyelid | Eyelid naevus | Paraneoplastic retinopathy |
| Benign neoplasm of lacrimal duct | Eyelid oedema | Parinaud syndrome |
| Benign neoplasm of lacrimal gland | Eyelid pain | Parophthalmia |
| Benign neoplasm of optic nerve | Eyelid ptosis | Pars plana cyst |
| Benign neoplasm of orbit | Eyelid ptosis congenital | Pathologic myopia |
| Benign neoplasm of retina | Eyelid rash | Periorbital abscess |
| Bickerstaff's encephalitis | Eyelid retraction | Periorbital cellulitis |
| Binocular eye movement disorder | Eyelid sensory disorder | Periorbital disorder |
| Birdshot chorioretinopathy | Eyelid skin dryness | Periorbital fat atrophy |
| Blau syndrome | Eyelid thickening | Periorbital fat herniation |
| Blebitis | Eyelid tumour | Periorbital haematoma |
| Blepharal papilloma | Eyelid vascular disorder | Periorbital haemorrhage |
| Blepharal pigmentation | Eyelid vellus hair changes | Periorbital infection |
| Blepharitis | Eyelids pruritus | Periorbital inflammation |
| Blepharitis allergic | Faciodigitogenital dysplasia | Periorbital oedema |
| Blepharochalasis | Fat adherence syndrome | Persistent corneal epithelial defect |
| Blepharophimosis | Fibrin deposition on lens postoperative | Persistent pupillary membrane |
| Blepharophimosis congenital | Filariasis | PHACES syndrome |
| Blepharospasm | Flat anterior chamber of eye | Phacolytic glaucoma |
| Blepharosynechia | Floppy eyelid syndrome | Phakomatosis |
| Blindness | Floppy iris syndrome | Photoelectric conjunctivitis |
| Blindness congenital | Foreign body in eye | Photokeratitis |
| Blindness cortical | Foreign body sensation in eyes | Photophobia |
| Blindness day | Foster-Kennedy Syndrome | Photopsia |
| Blindness hysterical | Fraser syndrome | Pigment dispersion syndrome |
| Blindness transient | Fuchs' syndrome | Pigmentary glaucoma |
| Blindness traumatic | Fungal retinitis | Pinguecula |
| Blindness unilateral | Gaze palsy | Pingueculitis |
| Bloch-Sulzberger syndrome | Giant papillary conjunctivitis | Polypoidal choroidal vasculopathy |
| Borderline glaucoma | Glare | Post measles blindness |
| Bowman's membrane disorder | Glassy eyes | Posterior capsule opacification |
| Bowman's membrane injury | Glaucoma | Posterior capsule rupture |
| Brow ptosis | Glaucoma traumatic | Posterior segment of eye anomaly |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Candida endophthalmitis | Glaucomatocyclitic crises | Posterior segment of eye anomaly congenital |
| Candida retinitis | Glaucomatous optic disc atrophy | Presbyopia |
| CANVAS syndrome | Graft versus host disease in eye | Presumed ocular histoplasmosis syndrome |
| Capsular block syndrome | Growth of eyelashes | Progressive external ophthalmoplegia |
| Carcinoma in situ of eye | Haemangioma of retina | Prominent epicanthal folds |
| Cataract | Halo vision | Prostaglandin analogue periorbitopathy |
| Cataract congenital | Heerfordt's syndrome | Protozoal corneal ulcer |
| Cataract cortical | Hemianopia | Pseudo-blepharoptosis |
| Cataract diabetic | Hemianopia heteronymous | Pseudoendophthalmitis |
| Cataract nuclear | Hemianopia homonymous | Pseudomyopia |
| Cataract operation complication | Hepato-lenticular degeneration | Pseudopapilloedema |
| Cataract subcapsular | Hereditary choroidal dystrophy | Pseudophakic bullous keratopathy |
| Cataract traumatic | Hereditary optic atrophy | Pseudophakic glaucoma |
| Cavernous sinus syndrome | Hereditary retinal dystrophy | Pseudophakodonesis |
| Cellulitis orbital | Hermansky-Pudlak syndrome | Pseudopterygium |
| Chalazion | Herpes ophthalmic | Pseudostrabismus |
| CHARGE syndrome | Herpes simplex necrotising retinopathy | Pseudoxanthoma elasticum |
| Charles Bonnet syndrome | Herpes simplex virus conjunctivitis neonatal | Psychogenic visual disorder |
| Chemical burns of eye | Herpes zoster necrotising retinopathy | Pterygium |
| Chemical eye injury | Heterochromia iridis | Punctate keratitis |
| Chemical iritis | Heteronymous diplopia | Pupil fixed |
| Chiasma syndrome | Heterophoria | Pupillary block |
| Chloropsia | Hippus | Pupillary deformity |
| Cholesterolosis bulbi | Holmes-Adie pupil | Pupillary disorder |
| Chorioretinal atrophy | Homonymous diplopia | Pupillary reflex impaired |
| Chorioretinal degeneration congenital | Hordeolum | Pupillotonia |
| Chorioretinal disorder | Horner's syndrome | Pupils unequal |
| Chorioretinal folds | Hyalosis asteroid | Purtscher retinopathy |
| Chorioretinal scar | Hypermetropia | Quadrantanopia |
| Chorioretinitis | Hypertelorism of orbit | Radiation cataract |
| Choroid melanoma | Hyphaema | Radiation corneal injury |
| Choroid neoplasm | Hypoaesthesia eye | Radiation retinopathy |
| Choroid tubercles | Hypopigmentation of eyelid | Raymond-Cestan syndrome |
| Choroidal coloboma | Hypopyon | Recession of chamber angle of eye |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Choroidal detachment | Hypotelorism of orbit | Refraction disorder |
| Choroidal dystrophy | Hypotony of eye | Refractive amblyopia |
| Choroidal effusion | Idiopathic orbital inflammation | Retinal aneurysm |
| Choroidal haemangioma | IIIrd nerve disorder | Retinal aneurysm rupture |
| Choroidal haematoma | IIIrd nerve injury | Retinal anomaly congenital |
| Choroidal haemorrhage | IIIrd nerve paralysis | Retinal arteriovenous malformation |
| Choroidal infarction | IIIrd nerve paresis | Retinal artery embolism |
| Choroidal neovascularisation | Immune recovery uveitis | Retinal artery occlusion |
| Choroidal rupture | Inclusion conjunctivitis | Retinal artery spasm |
| Choroidal sclerosis | Inclusion conjunctivitis neonatal | Retinal artery stenosis |
| Choroiditis | Infectious crystalline keratopathy | Retinal artery thrombosis |
| Chromatopsia | Infectious iridocyclitis | Retinal collateral vessels |
| Ciliary body degeneration | Infective corneal ulcer | Retinal coloboma |
| Ciliary body disorder | Infective episcleritis | Retinal cyst |
| Ciliary body haemorrhage | Infective iritis | Retinal degeneration |
| Ciliary hyperaemia | Infective keratitis | Retinal depigmentation |
| Ciliary muscle spasm | Infective scleritis | Retinal deposits |
| Ciliary zonular dehiscence | Infective uveitis | Retinal disorder |
| Closed globe injury | Inflammation of lacrimal passage | Retinal drusen |
| Cockayne's syndrome | Injury corneal | Retinal dystrophy |
| Cogan's syndrome | Injury of conjunctiva | Retinal exudates |
| Cohen syndrome | Intra-ocular injection complication | Retinal fibrosis |
| Coloboma | Intraocular haematoma | Retinal haemorrhage |
| Colour blindness | Intraocular melanoma | Retinal infarction |
| Colour blindness acquired | Iridocele | Retinal infiltrates |
| Commotio retinae | Iridocorneal endothelial syndrome | Retinal injury |
| Computer vision syndrome | Iridocyclitis | Retinal ischaemia |
| Congenital astigmatism | Iridodialysis | Retinal melanocytoma |
| Congenital choroidal anomaly | Iridodonesis | Retinal melanoma |
| Congenital corneal anomaly | Iridoplegia | Retinal migraine |
| Congenital epiblepharon | Iridoschisis | Retinal neoplasm |
| Congenital eye disorder | Iris adhesions | Retinal neovascularisation |
| Congenital eye naevus | Iris atrophy | Retinal oedema |
| Congenital eyelid malformation | Iris bombe | Retinal pallor |
| Congenital Horner's syndrome | Iris coloboma | Retinal perivascular sheathing |
| Congenital iris anomaly | Iris convex | Retinal phototoxicity |
| Congenital lacrimal gland anomaly | Iris cyst | Retinal pigment epithelial tear |
| Congenital lacrimal passage anomaly | Iris disorder | Retinal pigment epitheliopathy |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Congenital lenticonus | Iris exfoliation | Retinal pigmentation |
| Congenital myopia | Iris haemorrhage | Retinal scar |
| Congenital night blindness | Iris hyperpigmentation | Retinal tear |
| Congenital nystagmus | Iris hypopigmentation | Retinal telangiectasia |
| Congenital oculomotor apraxia | Iris incarceration | Retinal thickening |
| Congenital optic nerve anomaly | Iris injury | Retinal toxicity |
| Congenital retinoblastoma | Iris melanoma | Retinal vascular disorder |
| Congenital scleral disorder | Iris neoplasm | Retinal vascular occlusion |
| Congenital trichomegaly | Iris neovascularisation | Retinal vascular thrombosis |
| Congenital visual acuity reduced | Iris transillumination defect | Retinal vasculitis |
| Congenital vitreous anomaly | Iris vascular disorder | Retinal vein occlusion |
| Conjunctival abrasion | Iritis | Retinal vein thrombosis |
| Conjunctival adhesion | Irlen syndrome | Retinal vessel avulsion |
| Conjunctival bleb | IRVAN syndrome | Retinal white without pressure |
| Conjunctival cyst | IVth nerve disorder | Retinitis |
| Conjunctival degeneration | IVth nerve injury | Retinitis histoplasma |
| Conjunctival deposit | IVth nerve paralysis | Retinitis pigmentosa |
| Conjunctival discolouration | Kayser-Fleischer ring | Retinitis viral |
| Conjunctival disorder | Kearns-Sayre syndrome | Retinoblastoma |
| Conjunctival erosion | Keratic precipitates | Retinopathy congenital |
| Conjunctival filtering bleb leak | Keratitis | Retinopathy haemorrhagic |
| Conjunctival follicles | Keratitis bacterial | Retinopathy hypertensive |
| Conjunctival granuloma | Keratitis fungal | Retinopathy hyperviscosity |
| Conjunctival haemorrhage | Keratitis interstitial | Retinopathy of prematurity |
| Conjunctival hyperaemia | Keratitis sclerosing | Retinopathy proliferative |
| Conjunctival irritation | Keratitis viral | Retinopathy sickle cell |
| Conjunctival laceration | Keratitis-ichthyosis-deafness syndrome | Retinopathy solar |
| Conjunctival lymphangiectasia | Keratoconjunctivitis measles | Retinoschisis |
| Conjunctival melanoma | Keratoconus | Retinoschisis congenital |
| Conjunctival neoplasm | Keratomalacia | Retro-orbital neoplasm |
| Conjunctival oedema | Keratopathy | Rhegmatogenous retinal detachment |
| Conjunctival opacity | Keratorhexis | Rheumatoid scleritis |
| Conjunctival pallor | Keratosis gonococcal | Romana's sign |
| Conjunctival pigmentation | Keratouveitis | Ross syndrome |
| Conjunctival primary acquired melanosis | Koeppe nodules | Saccadic eye movement |
| Conjunctival retraction | Lacrimal atrophy | Schlemm's canal obstruction |
| Conjunctival scar | Lacrimal cyst | Scintillating scotoma |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Conjunctival telangiectasia | Lacrimal disorder | Scleral cyst |
| Conjunctival ulcer | Lacrimal duct neoplasm | Scleral degeneration |
| Conjunctival vascular disorder | Lacrimal duct pigmentation | Scleral deposits |
| Conjunctivalisation | Lacrimal fistula | Scleral discolouration |
| Conjunctivitis | Lacrimal gland abscess | Scleral disorder |
| Conjunctivitis allergic | Lacrimal gland enlargement | Scleral haemorrhage |
| Conjunctivitis bacterial | Lacrimal haemorrhage | Scleral hyperaemia |
| Conjunctivitis chlamydial | Lacrimal mucocoele | Scleral oedema |
| Conjunctivitis fungal | Lacrimal passage granuloma | Scleral pigmentation |
| Conjunctivitis gonococcal neonatal | Lacrimal punctum agenesis | Scleral thinning |
| Conjunctivitis tuberculous | Lacrimal punctum enlarged | Scleritis |
| Conjunctivitis viral | Lacrimal sac cellulitis | Scleritis allergic |
| Conjunctivochalasis | Lacrimal structural disorder | Scleromalacia |
| Contact lens acute red eye | Lacrimal structure injury | Seasonal allergy |
| Contact lens intolerance | Lacrimation decreased | Septo-optic dysplasia |
| Corectopia | Lacrimation disorder | Silent sinus syndrome |
| Cornea verticillata | Lacrimation increased | Sjogren's syndrome |
| Corneal abrasion | Lagophthalmos | Slipped extraocular muscle |
| Corneal abscess | Laurence-Moon-Bardet-Biedl syndrome | Spherophakia |
| Corneal bleeding | Leber's congenital amaurosis | Spontaneous hyphaema |
| Corneal cyst | Lecithin-cholesterol acyltransferase deficiency | Staphylococcal blepharitis |
| Corneal decompensation | Lens abnormality, congenital | Staphyloma |
| Corneal defect | Lens discolouration | Stargardt's disease |
| Corneal degeneration | Lens dislocation | Stickler's syndrome |
| Corneal deposits | Lens disorder | Strabismus |
| Corneal disorder | Lenticular injury | Strabismus congenital |
| Corneal dystrophy | Lenticular opacities | Sturge-Weber syndrome |
| Corneal endothelial cell loss | Lenticular pigmentation | Subacute myelo-opticoneuropathy |
| Corneal endotheliitis | Leukaemic retinopathy | Subconjunctival cyst |
| Corneal epithelial microcysts | Leukocoria | Subretinal fibrosis |
| Corneal epithelial wrinkling | Lid lag | Subretinal haematoma |
| Corneal epithelium defect | Lid margin discharge | Sudden visual loss |
| Corneal erosion | Lid sulcus deepened | Superficial injury of eye |
| Corneal exfoliation | Ligneous conjunctivitis | Superior corneal epithelial arcuate lesion |
| Corneal flap complication | Limbal stem cell deficiency | Superior limbic keratoconjunctivitis |
| Corneal graft rejection | Limbal swelling | Susac's syndrome |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Corneal hypertrophy | Lipaemia retinalis | Swollen tear duct |
| Corneal infection | Lipodermoid tumour | Symblepharon |
| Corneal infiltrates | Loss of visual contrast sensitivity | Sympathetic ophthalmia |
| Corneal irritation | Macrocornea | Tear discolouration |
| Corneal lesion | Macular cyst | Temporal arteritis |
| Corneal leukoma | Macular degeneration | Tenon's cyst |
| Corneal neovascularisation | Macular dystrophy congenital | Terrien's marginal degeneration |
| Corneal oedema | Macular fibrosis | Thermal burns of eye |
| Corneal opacity | Macular hole | Thyrotoxic crisis |
| Corneal opacity congenital | Macular ischaemia | Tilted disc syndrome |
| Corneal perforation | Macular oedema | Tolosa-Hunt syndrome |
| Corneal pigmentation | Macular opacity | Toxic anterior segment syndrome |
| Corneal scar | Macular pigmentation | Toxic cataract |
| Corneal staphyloma | Macular pseudohole | Toxic optic neuropathy |
| Corneal striae | Macular rupture | Toxocariasis |
| Corneal thickening | Macular scar | Trachoma |
| Corneal thinning | Macular vasospasm | Tractional retinal detachment |
| Corneal touch | Maculopathy | Traumatic iritis |
| Corneal warpage | Madarosis | Trichiasis |
| Corneoconjunctival intraepithelial neoplasia | MAGIC syndrome | Trichomegaly |
| Cortical visual impairment | Malignant exophthalmos | Triple A syndrome |
| Cri du Chat syndrome | Malignant glaucoma | Trisomy 13 |
| Crocodile tears syndrome | Malignant melanoma of eyelid | Trisomy 22 |
| Cryptophthalmos | Malignant neoplasm of choroid | Tuberculosis of eye |
| Cutaneous horn of eyelid | Malignant neoplasm of conjunctiva | Tubulointerstitial nephritis and uveitis syndrome |
| Cyanopsia | Malignant neoplasm of cornea | Tunnel vision |
| Cyclitic membrane | Malignant neoplasm of eye | Uhthoff's phenomenon |
| Cyclitis | Malignant neoplasm of eyelid | Ulcerative keratitis |
| Cyclopia | Malignant neoplasm of lacrimal duct | Usher's syndrome |
| Cycloplegia | Malignant neoplasm of lacrimal gland | Uveal prolapse |
| Cystic eyeball, congenital | Malignant neoplasm of orbit | Uveitic glaucoma |
| Cystoid macular oedema | Malignant neoplasm of retina | Uveitis |
| Cytomegalovirus chorioretinitis | Marcus Gunn syndrome | Uveitis-glaucoma-hyphaema syndrome |
| Dacryoadenitis acquired | Marfan's syndrome | Varicella keratitis |
| Dacryocanaliculitis | Meibomian gland discharge | Venous stasis retinopathy |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Dacryocystitis | Meibomian gland dysfunction | Vernal keratoconjunctivitis |
| Dacryolith | Meibomianitis | Vestibular nystagmus |
| Dacryostenosis acquired | Metallosis of globe | Viral corneal ulcer |
| Dacryostenosis congenital | Metamorphopsia | Viral keratouveitis |
| Dark circles under eyes | Metastases to eye | Viral uveitis |
| Deep anterior chamber of the eye | Metastatic ocular melanoma | Vision abnormal neonatal |
| Deformity of orbit | Microcornea | Vision blurred |
| Delayed dark adaptation | Microphthalmos | Visual acuity reduced |
| Delayed light adaptation | Microvascular cranial nerve palsy | Visual acuity reduced transiently |
| Delayed visual maturation | Mikulicz's disease | Visual brightness |
| Dellen | Mikulicz's syndrome | Visual cortex atrophy |
| Deposit eye | Millard-Gubler syndrome | Visual field defect |
| Detached Descemet's membrane | Miller Fisher syndrome | Visual impairment |
| Developmental glaucoma | Miosis | Visual pathway disorder |
| Diabetic blindness | Mittendorf dot | Visual perseveration |
| Diabetic eye disease | Morning glory syndrome | Visual snow syndrome |
| Diabetic glaucoma | Mycotic corneal ulcer | Vitamin A deficiency eye disorder |
| Diabetic keratopathy | Mycotic endophthalmitis | Vitamin A deficiency related conjunctival disorder |
| Diabetic ophthalmoplegia | Mydriasis | Vitamin A deficiency related corneal disorder |
| Diabetic retinal oedema | MYH9-related disease | VIth nerve disorder |
| Diabetic retinopathy | Myopia | VIth nerve injury |
| Diabetic uveitis | Myopic chorioretinal degeneration | VIth nerve paralysis |
| Diffuse lamellar keratitis | Myopic disc | VIth nerve paresis |
| Diffuse uveal melanocytic proliferation | Narrow anterior chamber angle | Vitreal cells |
| Diplopia | Necrotising herpetic retinopathy | Vitreomacular interface abnormal |
| Disorder of globe | Necrotising retinitis | Vitreous abscess |
| Disorder of orbit | Necrotising scleritis | Vitreous adhesions |
| Distichiasis | Neoplasm of cornea unspecified malignancy | Vitreous cyst |
| Dry age-related macular degeneration | Neoplasm of orbit | Vitreous degeneration |
| Dry eye | Neovascular age-related macular degeneration | Vitreous detachment |
| Duane's syndrome | Neurologic neglect syndrome | Vitreous disorder |
| Dyschromatopsia | Neurological eyelid disorder | Vitreous fibrin |
| Dysmetropsia | Neuromyelitis optica pseudo relapse | Vitreous floaters |
| Eales' disease | Neuromyelitis optica spectrum disorder | Vitreous haematoma |

| SOC Eye Disorders | SOC Eye Disorders | SOC Eye Disorders |
|---|---|---|
| Eccentric fixation | Neuropathy, ataxia, retinitis pigmentosa syndrome | Vitreous haemorrhage |
| Ectropion | Neurotrophic keratopathy | Vitreous haze |
| Ectropion uveae | Nictitating spasm | Vitreous injury |
| Eczema eyelids | Night blindness | Vitreous loss |
| Emanuel syndrome | Non-infectious endophthalmitis | Vitreous opacities |
| Endocrine ophthalmopathy | Noninfective chorioretinitis | Vitreous prolapse |
| Endophthalmitis | Noninfective conjunctivitis | Vitritis |
| Enophthalmos | Noninfective retinitis | Vogt-Koyanagi-Harada syndrome |
| Enophthalmos traumatic | Normal tension glaucoma | Waardenburg syndrome |
| Entropion | Norrie's disease | Wagner's disease |
| Entropion congenital | Nystagmus | Weill-Marchesani syndrome |
| Episcleral hyperaemia | Ocular albinism | Wildervanck syndrome |
| Episcleritis | Ocular cancer metastatic | Winchester syndrome |
| Erythema of eyelid | Ocular discomfort | Wolfram syndrome |
| Erythropsia | Ocular dysmetria | Wyburn Mason's syndrome |
| Eversion of lacrimal punctum | Ocular fistula | Xanthopsia |
| Excessive eye blinking | Ocular haemangiopericytoma | Xerophthalmia |
| Excessive ocular convergence | Ocular hyperaemia | Zika virus associated ocular birth defect |
| Exfoliation glaucoma | Ocular hypertension | Ocular icterus |

## 5.9 Minimum Critical Toxicities

Minimum Critical Toxicity search strategies are per SMQs and utilize MedDRA 21.0. As SMQs are standardized lists of PTs per MedDRA version, the individual SMQ PTs are not enumerated further within this document. The search strategies described below will be used to identify cases for analysis purposes and are not intended to be used to calculate frequencies of adverse drug reactions.

**Table 11: Table of Minimal Critical Toxicities and SMQ Search Strategies**

| Minimal Critical Toxicity | Search Strategy |
|---|---|
| Hepatotoxicity | • Biliary system related investigations, signs, and symptoms SMQ [narrow, broad]<br>• Cholestasis and jaundice of hepatic origin SMQ [narrow, broad]<br>• Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ [narrow, broad]<br>• Hepatitis, non-infectious SMQ [narrow, broad]<br>• Liver related investigations, signs and symptoms SMQ [narrow, broad] |
| Cardiac Toxicity | • Torsade de Pointes / QT prolongation SMQ [narrow, broad] |
| Nephrotoxicity | • Acute renal failure SMQ [narrow, broad] |
| Haematologic Toxicities | • Haematopoietic cytopenias affecting more than one type of blood cell SMQ [narrow, broad]<br>• Haematopoietic erythropenia SMQ [narrow, broad]<br>• Haematopoietic leukopenia SMQ [narrow, broad]<br>• Haematopoietic thrombocytopenia SMQ [narrow, broad] |

## 5.10 CYP3A4 Inhibitors and Inducers

The list of CYP3A4 inducers and inhibitors are retrieved from the Drug Bank (Wishart 2017). Terms are coded based on WHODrug Enhanced + Herbals (HD/DDE) Mar2018 B3 global.

The coded concomitant medications which contained below preferred terms will be marked according to type (inhibitor/inducer)) and category (moderate/strong) with the exception that medication administered through topical, optic or aural routes will not be considered as inducers or inhibitors.

| Type | Category | Preferred Name/Generic Name | Type | Category | Preferred Term |
|---|---|---|---|---|---|
| Inhibitor | Moderate | AMIODARONE | Inducer | Moderate | AVASIMIBE |
| Inhibitor | Moderate | AMPRENAVIR | Inducer | Moderate | BEXAROTENE |
| Inhibitor | Moderate | ANASTROZOLE | Inducer | Moderate | BOSENTAN |
| Inhibitor | Moderate | APREPITANT | Inducer | Moderate | DABRAFENIB |
| Inhibitor | Moderate | BARNIDIPINE | Inducer | Moderate | EFAVIRENZ |
| Inhibitor | Moderate | BENIDIPINE | Inducer | Moderate | ETRAVIRINE |
| Inhibitor | Moderate | CLOBAZAM | Inducer | Moderate | MIFEPRISTONE |
| Inhibitor | Moderate | CLOZAPINE | Inducer | Moderate | MODAFINIL |
| Inhibitor | Moderate | CRIZOTINIB | Inducer | Moderate | NAFCILLIN |
| Inhibitor | Moderate | DANAZOL | Inducer | Strong | APALUTAMIDE |
| Inhibitor | Moderate | DESVENLAFAXINE | Inducer | Strong | CARBAMAZEPINE |
| Inhibitor | Moderate | DILTIAZEM | Inducer | Strong | DEXAMETHASONE |
| Inhibitor | Moderate | DIMETHYL SULFOXIDE | Inducer | Strong | ENZALUTAMIDE |
| Inhibitor | Moderate | DRONEDARONE | Inducer | Strong | FOSPHENYTOIN |
| Inhibitor | Moderate | ERYTHROMYCIN | Inducer | Strong | LUMACAFTOR |

| Type | Category | Preferred Name/Generic Name | Type | Category | Preferred Term |
|---|---|---|---|---|---|
| Inhibitor | Moderate | FLUCONAZOLE | Inducer | Strong | MIDOSTAURIN |
| Inhibitor | Moderate | FLUVOXAMINE | Inducer | Strong | MITOTANE |
| Inhibitor | Moderate | FOSAMPRENAVIR | Inducer | Strong | NEVIRAPINE |
| Inhibitor | Moderate | FOSNETUPITANT | Inducer | Strong | OXCARBAZEPINE |
| Inhibitor | Moderate | FUSIDIC ACID | Inducer | Strong | PENTOBARBITAL |
| Inhibitor | Moderate | HALOPERIDOL | Inducer | Strong | PHENOBARBITAL |
| Inhibitor | Moderate | IMATINIB | Inducer | Strong | PHENYTOIN |
| Inhibitor | Moderate | INDALPINE | Inducer | Strong | PRIMIDONE |
| Inhibitor | Moderate | ISAVUCONAZOLE | Inducer | Strong | RIFAMPICIN |
| Inhibitor | Moderate | ISAVUCONAZONIUM | Inducer | Strong | RIFAMYCIN |
| Inhibitor | Moderate | ISONIAZID | Inducer | Strong | RIFAXIMIN |
| Inhibitor | Moderate | ISRADIPINE | Inducer | Strong | RIMEXOLONE |
| Inhibitor | Moderate | LINAGLIPTIN | Inducer | Strong | HYPERICUM PERFORATUM |
| Inhibitor | Moderate | LOVASTATIN | Inducer | Strong | GLUCOCORTICOIDS |
| Inhibitor | Moderate | LULICONAZOLE | | | |
| Inhibitor | Moderate | MICONAZOLE | | | |
| Inhibitor | Moderate | MIFEPRISTONE | | | |
| Inhibitor | Moderate | MILNACIPRAN | | | |
| Inhibitor | Moderate | NETUPITANT | | | |
| Inhibitor | Moderate | NICARDIPINE | | | |
| Inhibitor | Moderate | NILVADIPINE | | | |
| Inhibitor | Moderate | PAROXETINE | | | |
| Inhibitor | Moderate | PRIMAQUINE | | | |
| Inhibitor | Moderate | RISPERIDONE | | | |
| Inhibitor | Moderate | SERTRALINE | | | |
| Inhibitor | Moderate | SIMEPREVIR | | | |
| Inhibitor | Moderate | TIOCONAZOLE | | | |
| Inhibitor | Moderate | VENETOCLAX | | | |
| Inhibitor | Moderate | VENLAFAXINE | | | |
| Inhibitor | Moderate | VERAPAMIL | | | |
| Inhibitor | Moderate | ZIMELDINE | | | |
| Inhibitor | Moderate | ZIPRASIDONE | | | |
| Inhibitor | Strong | ATAZANAVIR | | | |
| Inhibitor | Strong | BOCEPREVIR | | | |
| Inhibitor | Strong | CLARITHROMYCIN | | | |
| Inhibitor | Strong | CLOTRIMAZOLE | | | |
| Inhibitor | Strong | COBICISTAT | | | |
| Inhibitor | Strong | CONIVAPTAN | | | |

| Type | Category | Preferred Name/Generic Name | Type | Category | Preferred Term |
|---|---|---|---|---|---|
| Inhibitor | Strong | CURCUMIN | | | |
| Inhibitor | Strong | DANOPREVIR | | | |
| Inhibitor | Strong | DARUNAVIR | | | |
| Inhibitor | Strong | DELAVIRDINE | | | |
| Inhibitor | Strong | DILTIAZEM | | | |
| Inhibitor | Strong | ECONAZOLE | | | |
| Inhibitor | Strong | EFAVIRENZ | | | |
| Inhibitor | Strong | ELVITEGRAVIR | | | |
| Inhibitor | Strong | ERGOTAMINE | | | |
| Inhibitor | Strong | IDELALISIB | | | |
| Inhibitor | Strong | INDINAVIR | | | |
| Inhibitor | Strong | ITRACONAZOLE | | | |
| Inhibitor | Strong | KETOCONAZOLE | | | |
| Inhibitor | Strong | LOPERAMIDE | | | |
| Inhibitor | Strong | LOPINAVIR | | | |
| Inhibitor | Strong | MIBEFRADIL | | | |
| Inhibitor | Strong | MIDOSTAURIN | | | |
| Inhibitor | Strong | NALOXONE | | | |
| Inhibitor | Strong | NEFAZODONE | | | |
| Inhibitor | Strong | NELFINAVIR | | | |
| Inhibitor | Strong | NILOTINIB | | | |
| Inhibitor | Strong | POSACONAZOLE | | | |
| Inhibitor | Strong | RIBOCICLIB | | | |
| Inhibitor | Strong | RITONAVIR | | | |
| Inhibitor | Strong | SAQUINAVIR | | | |
| Inhibitor | Strong | STIRIPENTOL | | | |
| Inhibitor | Strong | TELAPREVIR | | | |
| Inhibitor | Strong | TELITHROMYCIN | | | |
| Inhibitor | Strong | TERFENADINE | | | |
| Inhibitor | Strong | TIPRANAVIR | | | |
| Inhibitor | Strong | TROLEANDOMYCIN | | | |
| Inhibitor | Strong | VORICONAZOLE | | | |

### 5.11 Phosphate Binders

All terms in the search strategy are based on WHODrug Enhanced + Herbals (HD/DDE) Mar2018 B3 Global.

| Preferred Name/Generic Name | Preferred Name/Generic Name | Preferred Name/Generic Name |
|---|---|---|
| CALCIUM CARBONATE | SEVELAMER HYDROCHLORIDE | ALUMINUM HYDROXIDE |
| CALCIUM POLYSTYRENE SULFONATE | SUCROFERRIC OXYHYDROXIDE | |
| SEVELAMER | FERRIC CITRATE | |
| SEVELAMER CARBONATE | LANTHANUM CARBONATE | |

## 6 REFERENCE

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