Clinical Development

QBGJ398-302

Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Upper Tract Urothelial Carcinoma (UTUC) and Urothelial Carcinoma of the Bladder (UCB) with FGFR3 Genomic Alterations

Statistical Analysis Plan

Author: PPD PPD PPD

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V 1.0	30 August 2019	Not Applicable
V 2.0 draft	December 2022	Update per brief CSR
V 2.0 final	February 2023	Incorporate comments, and finalize the SAP

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term/Definition
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
cfDNA	cell-free DNA
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
$C_{trough\ (min)}$	trough observed plasma concentration (before drug administration)
C_{ss}	average plasma concentration at steady-state
CRO	contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
EQ-5D	EuroQOL five dimensions questionnaire
FGFR3	fibroblast growth factor receptor 3
HR	hazard ratio
ICH	International Council for Harmonization
ITT	intent-to-treat
K-M	Kaplan Meier
LVEF	left ventricular ejection fraction
MFS	metastatis-free survival
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle invasive bladder cancer
NMIBC	non-muscle invasive bladder cancer
OS	overall survival
PD-L1	programmed death-ligand 1
PK	pharmacokinetics
PR	partial response
QLQ	quality of life questionnaire
QOL	quality of life
QTcF	QTc corrected by Fridericia's formula
R_{acc}	accumulation ratio calculated as C_{min} steady-state/C_{min}
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
UBC	urothelial carcinoma of the bladder

UTUC	upper tract urothelial carcinoma

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study QBGJ398-302 dated 19 May 2021. Consequent to the business decision by Helsinn Heatlcare SA (HCC) on 5 October 2022 to stop the distribution of TRUSELTIQ and to withdraw new drug and marketing authorization applications worldwide, the further development of infigratinib in oncology outside of China was terminated which subsequently led to the closure of this study. The decision was not made based on any efficacy or safety concerns. With the limited number of patients randomized, the number of disease-free survival events required to assess the efficacy objectives was not achieved to the futility of the study.

The scope of this plan includes the early terminated study analysis. The analyses detailed within this plan will describe the efficacy and safety (primary and secondary study objectives) observed in the limited patients enrolled of adjuvant treatment of infigratinib for subjects with invasive urothelial carcinoma with susceptible fibroblast growth factor receptor (FGFR)3 genetic alterations (mutations, and gene fusions or translocations [ie, rearrangements]; hereafter referred to collectively as "FGFR3 alterations").

The PK of infigratinib has been well described as part of the conditional approvals granted in the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangement as detected by an FDA-approved test. Given the study and development termination, neither the PK nor the other exploratory endpoints (QoL and cfDNA) will be described.

No interim analysis and sample size adjustments were conducted given the timing of the early termination of the study.

2 OBJECTIVES

2.1 Primary Objective

The primary objective is to determine if treatment with infigratinib improves centrally reviewed disease-free survival (DFS) compared with placebo treatment in subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations after nephro-ureterectomy, distal ureterectomy, or cystectomy.

2.2 Secondary Objectives

The secondary objectives include:

- To compare DFS including intraluminal low risk recurrence in subjects treated with infigratinib vs placebo.
- To compare metastasis-free survival (MFS) of subjects treated with infigratinib vs placebo.
- To compare the overall survival (OS) in subjects treated with infigratinib vs placebo.

- To compare the investigator-reviewed disease-free survival (DFS) of subjects treated with infigratinib vs placebo.

- To characterize the safety and tolerability of infigratinib when administered as postoperative adjuvant monotherapy.

2.3 Exploratory Objectives

The exploratory objectives are not conducted due to the abbreviated Clinical Study Report (CSR).

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 3 multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy of infigratinib in approximately 218 adult subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations who are within 120 days following 7ephron-ureterectomy, distal ureterectomy, or cystectomy and ineligible for cisplatin-based adjuvant chemotherapy or with residual disease after neoadjuvant therapy. The sample size can be potentially increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach (Mehta and Pocock 2011). Subjects with invasive urothelial carcinoma include subjects with invasive upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of the bladder (UBC). The interim analysis is actually not conducted because the study is early terminated by sponsor.

Subjects will be randomized 1:1 to receive oral infigratinib or placebo administered once daily for the first 3 weeks (21 days) of each 28-day cycle for 52 weeks or until local/regional invasive or metastatic recurrence, unacceptable toxicity, withdrawal of informed consent, or death. Subjects will be evaluated for tumor recurrence radiographically every 3 months for the first 24 months, and annually thereafter or until recurrence by blinded independent central review (BICR) (local/regional invasive or metastatic) or metastatic recurrence by investigator assessment, whichever comes later. For subjects with UTUC (ie, subjects with a bladder), cystoscopy and urine cytology will be performed at 3, 6, 9, and 12 months, then every 6 months up to 24 months, and then annually until subjects experience recurrence by BICR (local/regional invasive or metastatic) or metastatic recurrence by investigator assessment, whichever is later. After that time, subjects will be followed for survival status and use of anticancer therapy approximately every 6 months (via phone or office visit) up to 1 year, then annually thereafter for 1 year after the final DFS event goal is reached (ie, End of Study [EOS]).

3.2 Stratification Factors

Subjects will be stratified according to lymph node involvement (yes vs no), prior neoadjuvant chemotherapy (yes vs no), AJCC Stage ((y)pT2 vs (y)pT3-4), and disease (UTUC vs UBC). Approximately 218 subjects will be randomized across approximately 100 centers worldwide. After interim analysis, the sample size may be increase up to a total of 328 subjects.

3.3 Sample Size Considerations

Approximately 218 subjects will be initially randomized in this study in a double-blind fashion. The sample size can be potentially increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach (Mehta and Pocock 2011). The study will start with a group sequential design with one interim analysis at approximately 35 centrally reviewed DFS events (50% of the initial event goal). A Haybittle-Peto boundary will be used for the efficacy boundary with a fixed one-sided alpha (α) of 0.00005 spent at the interim analysis for DFS, and the rest of the alpha (one-sided α 0.025) spent at the primary DFS analysis. Though an efficacy boundary is specified for the interim DFS analysis, the trial will not stop at the interim analysis if the efficacy boundary is crossed. A Lan DeMets alpha spending function approximating O'Brien-Fleming boundary will be used for non-binding futility boundary. Assuming disease will recur in 46% of subjects in the first 2 years and a 5% yearly recurrence rate in the third year and beyond for the placebo group, the required sample size with initial group sequential design is approximately 218 subjects to reach 70 centrally reviewed DFS events in 4 years. This is assuming with three-year uniform enrollment, one-year follow-up, 10% yearly drop-out rate and a hazard ratio (HR) of 0.5 (2-year DFS 73% in infigratinib arm vs 54% in placebo arm). The sample size will provide approximately 80% power to detect a difference in DFS assuming an HR of 0.5 comparing infigratinib vs placebo, based on a log-rank test controlling type I error at one-sided 0.025.

At the interim analysis, the study uses an adaptive design promising zone approach (Mehta and Pocock 2011) to adjust sample size and event as needed. The details of the sample size adaptation method will be pre-specified in the adaptation plan. If no sample size adaption is needed at the interim analysis, the study is projected to reach the planned number of centrally reviewed DFS events (70) 4 years from the randomization of the first subject. If a sample size increase is deemed necessary based on the interim result and the promising zone approach, the sample size/centrally reviewed event goal will be increased by maximum of 50% (328/105). If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly timewise when the adjusted event goal is reached. The boundary to test centrally reviewed DFS when the adjusted event goal is reached will be based on the original boundaries of the initial group sequential design.

4 STUDY ENDPOINTS AND COVARIATES

4.1 Endpoints

The primary endpoint is:

- Centrally reviewed DFS, from date of randomization to local/regional invasive or metastatic recurrence or death due to any cause, whichever occurs earlier.

The secondary endpoints are:

- Investigator reviewed DFS including intraluminal low-risk recurrence, from date of randomization to any recurrence or death due to any cause, whichever occurs earlier.

- Investigator reviewed MFS, from date of randomization to metastatic recurrence or death due to any cause, whichever occurs earlier.

- OS (from randomization to death).

- Investigator reviewed DFS, from date of randomization to local/regional invasive or metastatic recurrence or death due to any cause, whichever occurs earlier.

- Type, frequency, and severity of adverse events and serious adverse events, laboratory abnormalities, and other safety findings.

5 HYPOTHESES

No hypotheses will be tested due to the brief CSR.

6 DEFINITIONS

Baseline

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

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

Investigational Product/Study Treatment

'Investigational product' or 'study treatment' is used to reference only infigratinib or placebo.

Long-term Follow-up Phase

The long-term follow-up phase begins after the safety follow-up visit and continues until death or full consent withdrawal. Efficacy assessments including radiographic assessments, cystoscopy and urine cytology will continue to be performed until recurrence by BICR (local/regional invasive or metastatic) or metastatic recurrence by investigator assessment, whichever comes later. Subjects who develop recurrence by BICR (local/regional invasive or metastatic) or metastatic recurrence by investigator assessment prior to the long-term follow-up phase will not be followed for disease status during the long-term follow-up phase. After that time, subjects will be followed for survival every 6 months for 1 year, then annually thereafter (via telephone or office visit) for 1 year after the time when the final DFS event goal is reached (ie, EOS).

Overall Survival Time (OS)

Overall survival time is calculated as the number of months from randomization to death (date of death - date of randomization + 1)/(365.25/12). Subjects who have not died (no record of death) or are lost to follow up will be censored at the date of last known to be alive. Subjects who

withdraw consent for study participation, including consent to be followed, will be censored on the date of withdrawal.

Metastasis-free Survival Time (MFS)

The investigator reviewed MFS is defined as the time from randomization to any metastatic recurrence as determined by the investigator or death due to any cause, whichever occurs earlier. Subjects without documented metastatic recurrence and are still alive, will be censored at the last radiology assessment, or at the time of randomization if no radiology disease assessments are performed after the baseline visit.

Disease-free Survival Time (DFS)

Disease-free survival time is calculated as the number of months from randomization to the date of local/regional invasive or metastatic recurrence or death due to any cause (referred as DFS event) ((date of DFS event - date of randomization + 1)/ (365.25/12)). Subjects without recurrence (local/regional invasive or metastatic) or death will be censored at the last radiology assessment if previous cystoscopy result within 6 months is negative for muscle invasive disease, otherwise, DFS will be censored at the last complete recurrence assessment. Subjects who have no disease assessments after baseline will be censored on the randomization date. The primary DFS endpoint will be based on the central review (BICR), while for the secondary endpoint, the investigator reviewed DFS will be based on investigator review.

DFS including intraluminal low risk recurrence

The investigator reviewed DFS including intraluminal low risk recurrence is defined as the time from randomization to any recurrence as determined by investigator, or death due to any cause, whichever occurs earlier. For subjects without documented recurrence and are still alive, they will be censored at the last complete disease assessment (or, if no disease assessments are performed after the baseline visit or no death has been recorded, at the time of randomization).

Relative dose intensity

The relative dose intensity is defined as cumulative actual dose a subject have received divided by the planned cumulative dose. For example, a subject takes study drug from Day 1 to Day 21 at 125 mg/day; then from Day 29 to Day 30 at 100 mg/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%.

Study Day 1

Study Day 1 is defined as the day of the first administration of study treatment after randomization.

Treatment Duration

Treatment duration is defined as last dose date – first dose date +1.

On Treatment Period

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

Treatment-emergent Adverse Event

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

7 ANALYSIS POPULATION

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

7.1 Intent to Treatment Population

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

7.2 Safety Population

The safety population includes all subjects who are randomized and receive at least 1 administration of infigratinib or placebo. Subjects will be analyzed by the treatment received.

7.3 Subgroup Analyses

The summaries of adverse events may be performed for subgroups, as appropriate, defined by

- Sex (male vs female)
- Age at study enrollment (< 65 years vs ≥65 years)
- Race

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Principles

With the limited number of patients randomized at the time of the decision to early terminate the study, the number of disease-free survival events required to assess the efficacy objectives was not achieved to the futility of the study. No formal inferential testing of efficacy will be done. In general, any values, such as those due to unit conversion, will be reported rounding to the same number of decimal places as the original data. Month or year converted from day will be reported rounding to one place after the decimal point.

In general, categorical variables will be summarized using counts and percent. Percent will be displayed to one place after the decimal point, with the exception of 100%, which will be displayed without additional decimal places.

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

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

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

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

8.2 Handling of Missing Data

Partial dates will be defined as dates that are missing certain elements of the date field. This may include missing information for the month, day, or year, or two of these elements, but not all three.

Partial dates for adverse events where the start day is missing will be imputed as the first day of the month unless the start month of the adverse event is the same as the month when the treatment is initiated. In this case, the start day will be imputed as first dose date. The adverse event will be counted as treatment emergent adverse event. If the month, year, both month and year, or the entire start date is missing, then no data imputation will be implemented. However, these events will be counted with regard to treatment adverse event as long as there is no clear evidence to indicate adverse event starts before first dose date or after last dose date +30 days.

In general, for all other partial missing dates, if day is missing, day 15 will be imputed. No other imputation will be done if month or year is missing.

8.3 Subject Accountability and Disposition

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

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

8.4 Demographic and Baseline Characteristics

Summary statistics will be provided for demographics (age, sex, race, age group [<65 vs ≥ 65 and <75 vs ≥ 75], region and other baseline disease characteristics including FGFR3 mutation/fusion status, details on the mutation/fusion, lymph node involvement, stage at initial diagnosis, time from initial diagnosis to randomization, UTUC vs UBC and histology.

8.5 Medical History

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

8.6 Prior Anti-cancer Therapy

Prior anticancer therapy will be summarized including prior neo-adjuvant chemotherapy (yes vs no), neo-adjuvant chemotherapy type, and other prior anticancer medication.

Prior cancer related surgery and its type will also be summarized, in addition to the time from the last prior cancer related surgery to randomization. Prior radiotherapy will be also summarized.

8.7 Protocol Deviations

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

8.8 Efficacy Analyses

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

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

8.9 Sensitivity Analyses

Sensitivity analysis will not be performed for the abbreviated CSR.

8.10 Safety Analyses

Analysis of safety will be performed on the safety analysis population. Study data will be monitored on an ongoing basis by the clinical study team to ensure subjects' safety. Additional safety reviews will be performed by the data monitoring committee (DMC) periodically throughout the study. These reviews will include all available data on incidence of adverse events, serious adverse events including deaths. Study data will be monitored by QED's Global Safety Organization on an ongoing basis throughout the course of the study to identify potential safety signals and new events of interest. Any unblinding of serious adverse events (SAEs) by Global Safety due to regulatory requirements will be shared with the DMC.

8.10.1 Adverse Events

Treatment emergent AEs will be summarized. Treatment emergent AEs include all AEs that start on or after the first dose day of the study treatment and up to last dose day of the study treatment +30 days. All AEs collected in the AE electronic case report form (eCRF) page will be listed with treatment-emergent AEs flagged. In the body of this SAP treatment-emergent AEs are simply referred to as AEs, unless otherwise specified.

Adverse events will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. A subject with different National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

The following summary tables will be provided by treatment arm:

- Overall summary of AEs including the number and percentage of subjects with any AE, any serious AE, any AE leading to dose reductions/interruptions, any AE leading to discontinuation, and fatal AE.
- Summary of AEs by SOC, PT, and worst grade
- Summary of treatment-related AEs by SOC, PT, and worst grade.
- Summary of Grade 3 or 4 AEs by SOC, PT, and worst grade.
- Summary of serious AEs by SOC, PT, and worst grade
- Summary of serious treatment-related AEs by SOC, PT, and worst grade
- Summary of all AEs by PT in descending order of frequency
- Summary of treatment-related AEs by PT in descending order of frequency
- Summary of all Grade 3 or 4 AEs by PT in descending order of frequency
- Summary of SAEs by PT in descending order of frequency
- Summary of treatment-related SAEs by PT in descending order of frequency
- Summary of Common (10%) TEAEs by System Organ Class, Preferred Term and Worst Grade
- Summary of AEs leading to study treatment discontinuation by SOC, PT and worst grade
- Summary of AEs leading to study treatment discontinuation by PT in descending order of frequency
- Summary of AEs leading to dose reduction/interruption by SOC, PT, and worst grade
- Summary of AEs leading to dose reduction/interruption by PT in descending order of frequency
- Summary of fatal AEs by SOC, PT, and worst grade;
- Summary of fatal AEs by PT in descending order of frequency

- Summary of Common (10%) TEAEs by Preferred Term

The following listings will be produced:

- All adverse events
- All serious adverse events

The adverse events of special interest (AESI) will also be summarized. AESIs will include, but are not limited to calcium-phosphate homeostastis – hypercalcemia, hyper- and hypo-phosphataemia, ocular toxicity, cardiac toxicity, acute pancreatitis, pathological fracture, and tissue calcification.

Deaths

The primary reason for death will be summarized for on-treatment deaths (death occurs on or after first administration day of study treatment and within last administration day of study treatment +30 days), post-treatment deaths (death occurs after last administration day of study treatment +30 days), and all deaths for the safety analysis population.

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

8.10.2 Concomitant Medications

Concomitant medications are defined as medications that subject have taken on or after the first administration day of study treatment and within the last administration day of study treatment +30 days. Concomitant mediations will be coded using the World Health Organization (WHODrug) dictionary and summarized by Anatomical Therapeutic Chemical (ATC) classification and PTs.

8.10.3 Treatment Exposure

Duration of study treatment (last dose date – first dose date+1) and cumulative dose will be summarized by treatment arm. In addition, the relative dose intensity (cumulative actual dose/planned cumulative dose) will be summarized.

The number of subjects with prescribed dose holds or dose reductions and the reason for prescribed dose hold/reduction will be tabulated by treatment group. The summary of actual dose changes other than prescribed and the reason will also be summarized.

8.10.4 Laboratory Data Summary

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

The laboratory summaries will include all lab assessments collected within the last administration day of study treatment +30 days. Laboratory parameters for hematology and blood chemistry will be summarized at baseline, selected post-baseline visit, the maximum and

minimum observed post-baseline values, and last observed value, along with the change from baseline. Lab shift tables will be done separately and labeled by direction.

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

8.10.5 Ophthalmic 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.

8.10.6 Left Ventricular Ejection Fraction (LVEF)

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%

8.10.7 ECG

The electrocardiogram (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, 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
- QTcB, or QTcF
  - New value of >450 ms
  - New value of >480 ms
  - New value of >500 ms
  - Increase from baseline of >30 ms to ≤60 ms
  - Increase from baseline of >60 ms
- Heart Rate (HR)
  - Increase from baseline >25% and to a value >100 bpm
  - Decrease from baseline >25% and to a value <50 bpm
- PR
  - Increase from baseline >25% and to a value >200 ms
- QRS
  - Increase from baseline >25% and to a value >100 ms

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

8.10.8 Vital Signs and ECOG Performance Status

Eastern Cooperative Oncololgy Group (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), the worst observed post-baseline values, and the last observed value, along with the change from baseline.

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

9 REFERENCE LIST

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10 APPENDIX

- 302 brief CSR TFL shell: in a separate document