STATISTICAL ANALYSIS PLAN

Protocol DCC-2618-03-001 (INVICTUS)

A Phase 3, INterVentional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with AdvanCed Gastrointestinal Stromal TUmorS who have Received Treatment with Prior Anticancer Therapies

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Deciphera Pharmaceuticals, LLC

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Final 2.0
08 Aug 2019

APPROVALS

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the study, and all applicable regulatory guidance and guidelines.

PI

08 Aug 2019

Prepared by: Date

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08 Aug 2019

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Reviewed and approved by: Date

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ABBREVIATIONS

Below is the list of acronyms that will be used throughout this document.

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC-2	Anatomical Therapeutic Chemical 2nd level
BID	Twice Daily
cfDNA	Cell-Free DNA
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item
EOT	End of Treatment
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EQ-VAS	EuroQol visual analogue scale
GIST	Gastrointestinal Stromal Tumors
IDMC	Independent Data Monitoring Committee
KM	Kaplan-Meier
ICH	International Conference on Harmonisation
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PR	Partial Response
PT	Preferred Term
PFS	Progression-Free Survival
PK	Pharmacokinetics
PP	Per Protocol
QD	Once daily
QOL	Quality of Life

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TTP	Time to Progression
VAS	Visual analogue scale
WHO	World Health Organization

SUMMARY OF MAJOR CHANGES

Section(s)	Version 1 Language	Version 2 Language	Rationale for Change
3.1	Double-blind treatment analysis period from the randomization date to the last follow-up date for patients who discontinued from the study upon disease progression by independent radiologic review on initial treatment or discontinuation from initial treatment due to other cause from the randomization date to the first disease progression date for patients who continued to receive DCC-2618 at 150mg QD or an escalated dose and those who crossed over from placebo to receive DCC-2618 at150mg QD after disease progression on initial treatment Open-label analysis period from the day immediately after the first disease progression on initial treatment to the last follow-up date for patients who continued to receive DCC-2618 150mg QD or at an escalated dose and those who crossed over from placebo to receive DCC-2618 150mg QD after disease progression on initial treatment	• Double-blind treatment analysis period o from the randomization date to the last follow-up date, ▪ if a patient did not have disease progression based on independent radiologic review, or, ▪ if a placebo patient did not cross over to DCC-2618 treatment, or, ▪ if a patient was initially treated with DCC-2618 and did not continue to receive DCC-2618 at 150mg QD or escalate to 150mg BID after disease progression based on independent radiologic review. o from the randomization date to the first disease progression date if a patient was initially treated with DCC-2618 and continued to receive DCC-2618 at 150mg QD after disease progression based on independent radiologic review. o from the randomization date to the day immediately before the first dose of DCC-2618 150mg BID if a patient was initially treated with DCC-2618 and escalated to DCC-2618 150mg BID after disease progression based on independent radiologic review. o from the randomization date to the day immediately before the first dose of DCC-2618 150mg QD if a patient crossed over from placebo to receive DCC-2618 at150mg QD after disease progression based on independent radiologic review. • Open-label analysis period o from the day immediately after the first disease progression based on independent radiologic review to the last follow-up date if a patient was initially treated with DCC-2618 and continued to receive DCC-2618 150mg QD after disease progression based on independent radiologic review. o from the first dose date of DCC-2618 150mg BID to the last follow-up date if a patient was initially treated with DCC-2618 and escalated to DCC-2618 150mg BID after disease progression based on independent radiologic review. o from the first dose date of DCC-2618 150mg QD to the last follow-up date if a patient crossed over from placebo to receive DCC-2618 150mg QD after disease progression based on independent radiologic review.	Revision for more specific definitions
3.5		Handling of Repeated and Unscheduled Assessments In general, for by-visit summaries, data recorded at nominal visits will be presented. Laboratories, vital signs, ECG, and ECHO/MUGA results at unscheduled visits and repeated assessments will not be included in the by-visit summaries however will contribute to the best/worst case value, and last on-treatment visit, where applicable. Tumor assessments at unscheduled visits will be used for the derivation of the primary endpoint and other efficacy endpoints.	Addition of a new section.

Section(s)	Version 1 Language	Version 2 Language	Rationale for Change
4.3	A Per Protocol (PP) population may be included if there are patients in the ITT population who have protocol violations that are expected to compromise the efficacy and/or safety assessments (eg, patients enrolled who do not meet key eligibility criteria during the study). At the primary efficacy analysis, protocol violators resulting in exclusion from the PP population will be identified by the sponsor and documented prior to the database freeze.	The Per Protocol (PP) population is defined as randomized patients who do not have important protocol deviations that are expected to compromise the efficacy and/or safety assessments as follows, • Inclusion/exclusion criteria deviations • Patient receiving wrong treatment • Patient receiving incorrect dose • Patient receiving prohibited medications The criteria for the important protocol deviations will be determined by the sponsor and documented in a separate file.	Revision of the definition to align with ICH E3 R1 Guidelines 2013
6	A major protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being (ICH E3 R1 Guidelines 2013). All major deviations related to trial inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be described in the clinical study report.	In addition, the sponsor will determine the important protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being (ICH E3 R1 Guidelines 2013). Patients who have important deviations will be excluded from the Per-protocol population. All the important deviations will be summarized and described in the clinical study report.	Revision of the definition to align with ICH E3 R1 Guidelines 2013
8.1	For patients who have first disease progression or die after two or more consecutive missed/non-evaluable assessments , the patient will be censored at the time of the evaluable radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable radiologic assessments.	For patients who have first disease progression or die after two or more consecutive missed/non-evaluable assessments , the patient will be censored at the time of the evaluable radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable radiologic assessments. The missed/non-evaluable assessments include both the scheduled assessments when a patient was on treatment and the hypothetical assessments (the expected assessments as if the patient was still on treatment) after a patient discontinued treatment or withdrew for reasons other than progressed disease.	Addition to the handling rule of missing assessments in a hypothetic situation.
8.3.5	An analysis of covariance with study treatment, KIT/PDGFRA fourth line/KIT/PDGFRA fifth line/PDGFRA D842V status, and ECOG status at baseline will be performed.		Remove of the originally planned analysis of EORTC-QLQ-C30 which was not appropriate. Addition of new analysis to EQ-5D-5L.

Section(s)	Version 1 Language	Version 2 Language	Rationale for Change
8.3.5	Score sets are available for Denmark, France, Germany, Japan, Netherlands, Spain, UK, US and Zimbabwe. For countries in which no score set exists (Canada, Hungary, Israel, Romania, and Sweden) the closest neighboring country will be used as a proxy (EuroQol Group, 2015). EQ-5D-5L will be summarized overall by n and percentage for each level of each dimension. The Cochran–Mantel–Haenszel test will be used to test differences between DCC-2618 and placebo. The EuroQol visual analogue scale (EQ-VAS) is a measure of overall self-rated health status, used and analyzed separately from the index score. The EQ-VAS recorded the subject's self-rated health on a 20 cm vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine." The EQ-VAS score ranges from 0 to 100, with higher scores indicative of better overall health. EQ-VAS will be summarized using continuous descriptive. statistics.	Score sets are available for Denmark, France, Germany, Japan, Netherlands, Spain, UK, US and Zimbabwe. For countries in which no score set exists (Canada, Hungary, Israel, Romania, and Sweden) the closest neighboring country will be used as a proxy (EuroQol Group, 2015), eg, UK value set for Australia, France value set for Belgium, USA value set for Canada and Singapore, and Germany value set for Poland. If scale is missing for one of the dimensions, the index (utility) score will have a missing value. EQ-5D-5L will be summarized overall by number and percentage for each level of each dimension. For pain/discomfort and usual activities, the Cochran–Mantel–Haenszel test will be used to test the change in response scale at Day 1 of Cycle 2 from baseline between DCC-2618 and placebo. For EQ-5D-5L index (utility) score, an ANCOVA model with the stratification factors as factors will be used to compare the change at Day 1 of Cycle 2 from baseline between the two treatment arms. The EuroQol visual analogue scale (EQ-VAS) is a measure of overall self-rated health status, used and analyzed separately from the index score. The EQ-VAS recorded the subject's self-rated health on a 20 cm vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine." The EQ-VAS score ranges from 0 to 100, with higher scores indicative of better overall health. EQ-VAS will be summarized using continuous descriptive statistics. Change in EQ-VAS score at Day 1 of Cycle 2 from baseline between the two treatment arms will be tested with a t-test.	Addition of the use of value sets and corresponding new analyses to EQ-5D-5L.
8.3.7		8.3.7 Duration of Response Duration of response is defined as the time interval from the first assessment of confirmed CR or PR until the first disease progression or death. In the case that the PFS is censored, duration of response will be censored at the last evaluable progression-free radiologic assessment in an analogous manner. Duration of response based on the independent radiologic review will be analyzed with Kaplan-Meier method using the 25th, 50th (median), and 75th percentiles and survival probability at pre-specified timepoints, each with associated 2-sided 95% confidence intervals. Duration of response based on the Investigator assessment will be analyzed in a similar fashion as well.	Addition of new efficacy endpoint and analysis.
10.4		Numeric laboratory values recorded as "<x" or ">x" will be handled as follows, • In the listings, "<x" and ">x" will be presented as recorded • In the summary tables of observed values and changes from the baseline and those for shifts in CTCAE grade, "<x" and ">x" will be converted to numeric values before the analysis, o "<x" will be converted to "x – 1e-6" o ">x" will be converted to "x + 1e-6" In the summary tables of numeric values, the convention is to present 1 decimal place beyond those used in raw data for median and mean and 2 more decimal places beyond those	Addition to handle the data that are not entered in a normal way.

Section(s)	Version 1 Language	Version 2 Language	Rationale for Change
		used in raw data for standard deviation and standard error. There will be no deviation from this convention to display 6 or more decimals due to any conversion using the above rules.	
11.4	Efficacy data during the open-label analysis period will be presented in listings only.	Efficacy analysis during the open-label analysis period will be explored by analysis sub-periods. For patients who initially received placebo and subsequently crossed over to DCC-2618 treatment, PFS in the "Prior to intra-patient dose escalation" sub-period will be defined as the time interval between the date of first dose of DCC-2618 and the earliest documented evidence of disease progression. PFS will be re-defined or censored as needed, and analyzed in a similar fashion to the primary efficacy endpoint. For patients in the "Intra-patient dose escalation" sub-period, efficacy assessment data will be presented in listings only.	Addition of new efficacy analysis.

1 INTRODUCTION

This statistical analysis plan (SAP) describes the methods to be used in the analysis of study data from clinical protocol DCC-2618-03-001 (invictus) in order to answer the study objectives, and is based on Amendment 5 of the study protocol, dated 30Oct2018.

Populations for analysis, data handling rules, and statistical methods are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial. Pharmacokinetic (PK) analysis, pharmacodynamic (PD) and bioanalytical data analysis is not in the scope of this SAP. These analyses will be separately planned and reported. The SAP outlines any differences in data analysis methods relative to those planned in the study protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

2 OVERALL STUDY DESIGN AND OBJECTIVES

2.1 Study Objectives

2.1.1 Primary Objective

To assess the efficacy (progression-free survival [PFS]) of DCC-2618 by independent radiologic review in patients with advanced gastrointestinal stromal tumors (GIST) who have received prior therapies

2.1.2 Key Secondary Objective

To assess objective response rate (ORR) by independent radiologic review

2.1.3 Additional Secondary Objectives

- To assess other parameters of efficacy, including but not limited to time to progression (TTP) and overall survival (OS)
- To assess the PD/PK relationship of DCC-2618
- To assess the robustness of efficacy using a sensitivity analysis
- To assess improvement of disease-related symptoms and quality of life (QOL)
- To assess the safety of DCC-2618

2.1.4 Exploratory Objectives

- To assess the efficacy of DCC-2618 in patients after dose escalation to DCC-2618 150 mg twice daily (BID)
- To characterize KIT and PDGFRA gene resistance mutations (and potentially other gene mutations) and their DCC-2618-driven longitudinal mutation allele frequency changes in plasma cell-free DNA (cfDNA)
- To retrospectively correlate KIT and PDGFRA mutation/s and/or their frequency (as well as of potentially other gene mutations) in baseline cfDNA with clinical benefit
- To understand potential tyrosine kinase inhibitor- (TKI) resistance mechanisms of GIST at time of progression

- To determine concordance between KIT, PDGFRA, and other genetic mutations in tumor and cfDNA at baseline
- To assess healthcare utilization in patients with advanced GIST who have received approved therapies

2.2 Trial Design and Study Procedures

2.2.1 Study Design

This is a 2-arm, randomized, placebo-controlled, double-blind, international, multicenter study comparing the efficacy of DCC-2618+best supportive care to placebo+best supportive care in patients with advanced GIST who have received treatment with prior anticancer therapies. Prior anticancer therapies must include treatment with imatinib, sunitinib, and regorafenib (3 prior therapies). Up to 40% of enrolled patients may have received prior treatment with imatinib, sunitinib, regorafenib, and other drugs (≥4 prior therapies). Approximately 120 patients will be randomized in a 2:1 ratio to DCC-2618 150 mg once daily (QD) or placebo. Randomization will be stratified by the number of prior anticancer treatments (3 versus ≥4) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 versus 1 or 2).

The primary response to study treatment for the study will be evaluated using the modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 - GIST-specific (hereafter referred to as "modified RECIST") based on independent radiologic review.

2.2.2 Treatments and Assignment to Treatments

Approximately 120 patients will be randomized to 2:1 to 150 mg QD of DCC-2618 versus placebo. Randomization will be stratified by:

- Patients who have received 3 prior anticancer treatments versus patients who have received ≥4 prior anticancer treatments.
- ECOG performance status=0 versus ECOG performance status=1 or 2.

Patients will continue on the current treatment until the time of disease progression by modified RECIST from the independent radiological review, unacceptable toxicity, or withdraw of consent. Upon progression confirmation by independent radiological review, study treatment will be unblinded.

At that time:

Patients randomized to DCC-2618 150 mg QD will be given the option to:

- continue DCC-2618 at an increased dose of 150 mg BID, or
- continue treatment on study with the same dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or
- discontinue DCC-2618.

Patients randomized to placebo will be given the option to:

- cross over to receive DCC-2618 150 mg QD, or
- discontinue the study

Patients randomized to placebo who cross over to receive DCC-2618 150 mg QD and have disease progression by modified RECIST based on Investigator assessment will be given the option to:

- continue DCC-2618 at an increased dose of 150 mg BID
- continue treatment on study with the same DCC-2618 dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study) or
- discontinue DCC-2618.

2.3 Determination of Sample Size

The sample size selection of approximate 120 patients (n=80 DCC-2618, n=40 placebo) was based on considerations for powering of the primary endpoint, key secondary endpoint, detection of rare safety events and overall exposure to DCC-2618, and assuming 15% patient dropout. Patients will be randomized in a 2:1 ratio of DCC-2618 versus placebo.

This sample size [105 patients (n=70 DCC-2618, n=35 placebo) with 90 events (55 DCC-2618, 35 placebo) at the final analysis] will have at least 90% power to detect a difference in PFS between DCC-2618 and placebo assuming a median PFS of 4.5 months for DCC-2618 and 1 month for placebo. Moreover, this assumes 9 months of uniform recruitment and 6 additional months of follow-up (total patient follow-up of 15 months).

Furthermore, 105 patients (n=70 DCC-2618, n=35 placebo) will have approximately 80% power to detect a 0.2 difference in ORR assuming that the ORR for DCC-2618 = 0.22 and the ORR for placebo = 0.02.

In addition, a minimum sample size of 80 DCC-2618 patients allows adequate power to detect the incidence of rare safety events. A sample of 80 patients yields 95% probability that the study will reveal at least one occurrence of all safety events that occur in patients at a rate of 4.0% or greater. This in combination with the exposure to DCC-2618 from other studies conducted in this clinical program will meet the recommendations for overall exposure recommended by FDA.

Where required, safety personnel at the Sponsor or designee may be unblinded to a patient's study drug assignment to meet reporting requirements to regulatory agencies. In addition, the Investigator, patient, Sponsor, and study team will be unblinded at the time the patient has disease progression by modified RECIST based on independent radiology review.

At no point in time before official full study unblinding will any efficacy and safety analyses be conducted by the Sponsor or Sponsor representatives, unless there is explicit permission to do so, for instance high level efficacy assessment for the purposes of an Independent Data Monitoring Committee (IDMC) review to determine the adequacy of the risk/benefit profile of the drug as it pertains to the conduct of the clinical trial.

3 GENERAL ANALYSIS CONVENTIONS

Statistical analysis will be performed using SAS® (version 9.4 or newer).

3.1 Statistical Analysis Periods

Based on the study design, two main analysis periods will be defined as follows:

- Double-blind treatment analysis period
    - from the randomization date to the last follow-up date
        - if a patient did not have disease progression based on independent radiologic review or
        - if a placebo patient did not cross over to DCC-2618 treatment or
    - if a patient was initially treated with DCC-2618 and did not continue to receive DCC-2618 at 150mg QD or escalate to 150mg BID after disease progression based on independent radiologic review from the randomization date to the first disease progression date if a patient was initially treated with DCC-2618 and continued to receive DCC-2618 at 150mg QD after disease progression based on independent radiologic review
    - from the randomization date to the day immediately before the first dose of DCC-2618 150mg BID if a patient escalated to DCC-2618 150mg BID after disease progression based on independent radiologic review
    - from the randomization date to the day immediately before the first dose of DCC-2618 150mg QD if a patient crossed over from placebo to receive DCC-2618 at150mg QD after disease progression based on independent radiologic review
- Open-label analysis period
    - from the day immediately after the first disease progression based on independent radiologic review to the last follow-up date if a patient was initially treated with DCC-2618 and continued to receive DCC-2618 150mg QD after disease progression based on independent radiologic review
    - from the first dose date of DCC-2618 150mg BID to the last follow-up date if a patient was initially treated with DCC-2618 and escalated to DCC-2618 150mg BID after disease progression
    - from the first dose date of DCC-2618 150mg QD to the last follow-up date if a patient crossed over from placebo to receive DCC-2618 150mg QD after disease progression based on independent radiologic review

The primary efficacy endpoint, progression-free survival, will be defined and analyzed only during the double-blind treatment analysis period.

Overall survival will be defined and analyzed throughout patients' entire on study period. The data cut-off for the primary analysis will occur when 90 PFS events have occurred. It is expected that the primary analysis will occur approximately 6 months after the last patient is enrolled into the trial.

As of the primary efficacy analysis, the evaluation of the efficacy and safety of DCC-2618 against the placebo will be mainly based on the data collected during the double-blind treatment analysis period. The analysis during this period will be detailed in Sections 3.2 to 10.10.

For data collected during the open-label analysis period and entered in the database by the data cut-off date or at the final database lock, statistical analysis will be described in Section 11.

3.2 Visit Windows

The protocol visit windows are defined the same for blinded treatment and open label treatment phases. Visits will be analyzed per the electronic case report form (eCRF) collection. Unscheduled visits will be mapped to a scheduled visits if possible, using a window based on all the available actual visit dates for the scheduled visits.

Reference start date will be defined as Cycle 1 Day 1 visit date. Study Day will be calculated from the reference start date and used to show start/stop day of the assessments and events as follows,

- For assessments/events on/after the reference start date:

  Study Day= (date of assessment/event – reference start date) +1

- For assessments/events before the reference start date:

  Study Day= (date of assessment/event – reference start date)

3.3 Baseline

Unless specified otherwise, baseline measurements will be the most recent (ie, last non-missing) value collected from screening until prior to receiving the first dose of study medication (Cycle 1 Day 1).

3.4 Handling of Repeated and Unscheduled Assessments

In general, for by-visit summaries, data recorded at nominal visits will be presented.

Laboratories, vital signs, ECG, and ECHO/MUGA results at unscheduled visits and repeated assessments will not be included in the by-visit summaries however will contribute to the best/worst case value, and last on-treatment visit, where applicable.

Tumor assessments at unscheduled visits will be used for the derivation of the primary endpoint and other efficacy endpoints.

3.5 Coding Dictionaries

Medical history and adverse events (AE) will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1 or higher. Prior and concomitant medications and procedures will be coded using the World Health Organization (WHO) Drug Dictionary (SEP 2018) or higher.

3.6 General Analysis Conventions

Continuous variables will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and proportions. Time-to-event data will be summarized via Kaplan-Meier (KM) methodology using the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals.

4 ANALYSIS POPULATIONS

4.1 Intention-to-treat Population

The Intention-to-treat Population (ITT) population is defined as all patients who signed the informed consent and were randomized.

The ITT population will be used for all efficacy analysis as a primary analysis set with treatment assignment based on randomization.

4.2 Safety Population

The Safety population is defined as all patients who have received at least 1 dose of study drug.

The safety population will be used for all safety analyses with treatment actually received.

4.3 Per Protocol Population

The Per Protocol (PP) population is defined as randomized patients who do not have important protocol deviations that are expected to compromise the efficacy and/or safety assessments as follows,

- Inclusion/exclusion criteria deviations
- Patient receiving wrong treatment
- Patient receiving incorrect dose
- Patient receiving prohibited medications

The criteria for such important protocol deviations will be determined by the sponsor and documented in a separate file. At the primary efficacy analysis, protocol deviations resulting in exclusion from the PP population will be identified by the sponsor and documented prior to the database lock.

4.4 PK Population

The PK population will include all randomized subjects who received at least 1 dose of DCC-2618 and had at least 1 non-missing PK concentration in plasma reported for DCC-2618 or DP-5439.

The PK population will be used for all PK analyses.

5 PATIENT DISPOSITION

Patient disposition will be summarized overall for all patients who enrolled in the study (ie, signed the informed consent for the study and were randomized). In addition, the number of patients in each population (ie, ITT, safety, PK, and PP) will be displayed. The number and proportion of patients among the safety population who have discontinued from treatment and the study will be summarized along with the reason for discontinuation.

6 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the clinical protocol. Protocol deviations will be classified by medical review prior to primary analysis and major protocol deviations will be identified.

The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file). This file will include a description of each protocol deviation and whether or not this deviation is classified as a major protocol deviation. This file will be finalized prior to database lock and study unblinding.

In addition, the sponsor will determine the important protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being (ICH E3 R1 Guidelines 2013). Patients who have important deviations will be excluded from the Per-protocol population. All the important deviations will be summarized and described in the clinical study report.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

7.1 Demographic Characteristics

Demographic and baseline characteristics at study entry will be summarized for the safety and intention-to-treat populations.

Demographic and baseline variables to be summarized are:

- Continuous variables
  - Age (years) at time of consent
  - Height (cm)
  - Weight (kg)
- Categorical variables
  - Gender
  - Race
  - Ethnicity
  - Screening ECOG (stratification variable)
  - Number of prior therapies (stratification variable)

7.2 Medical History

The number and percentage of patients with each medical history condition will be summarized for the safety population by system organ class and preferred term as coded using MedDRA Version 21.1 or higher.

7.3 Cancer History and Prior Cancer Therapy

Histologic diagnosis of GIST, tumor mutation status, histology, stage at initial diagnosis, and time since the initial diagnosis in years (calculated from the informed consent date) will be summarized for the Safety Population. For prior cancer therapy, the number of patients and the type of systemic therapy, surgery, and radiation will be summarized along with the number of systemic therapy regimens per patient for the safety population.

8 EFFICACY ANALYSIS

8.1 Primary Efficacy Analysis

The primary endpoint of PFS (reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of the first disease progression based on the independent radiologic review or death due to any cause on initially assigned study treatment, whichever comes earlier. In the following situations, PFS will be re-defined otherwise or censored:

- For patients who do not have evaluable radiologic assessment (including those randomized but untreated due to death or any other cause), PFS will be censored at randomization date (PFS=1 day) unless they die within 2 cycles of treatment (8 weeks plus 3 days allowing for a late radiologic assessment within the visit window). If patients die within 2 cycles of treatment (8 weeks plus 3 days), they are considered to have a PFS event at death date
- For patients who only have non-measurable lesion according to modified RECIST Version 1.1 (non-nodal lesions must be ≥1.0 cm in the long axis or ≥double the slide thickness in the long axis) within 21 days prior to the first dose of study treatment, PFS will be censored at the date of latest evaluable progression-free radiologic assessment or patients will be considered to have disease progression at the date of new lesion(s) or unequivocal progression in non-target disease
- For patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments than the study treatment before documented date of the first disease progression, PFS will be censored at the date of the latest evaluable progression-free radiologic assessment
- For patients who have not progressed and have not died, PFS will be censored at the time of the latest date of evaluable progression-free radiologic assessment if at most one missed/non-evaluable assessment prior to this assessment
- For patients who have first disease progression or die after two or more consecutive missed/non-evaluable assessments , the patient will be censored at the time of the evaluable radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable radiologic assessments. The missed/non-evaluable assessments include both the scheduled assessments when a patient was on treatment and the hypothetical assessments (the expected assessments as if the patient was still on

treatment) after a patient discontinued treatment or withdrew for reasons other than progressed disease. For patients who have first disease progression documented between scheduled assessments, progression date is defined as the date of new lesion (if progression is due to new lesions) or defined as the earliest of the scan dates of the components that triggered the progression per independent radiologic review (if progression is due to increase in sum of measured lesions).

Analysis for PFS will be stratified by the randomization stratification factors [prior lines of therapy (3 versus ≥4) and ECOG (0 versus 1 or 2)] . The p-value will be from a 2-sided stratified Log-rank test at 0.05 significant level for evaluation of treatment difference. Point estimate of hazard ratio will be obtained from a Cox regression model with treatment and the randomization stratification factors as fixed factors and it's 95% CI will be obtained using Wald method. PFS time will be summarized via KM methodology using the 25th, 50th (median), and 75th percentiles and pre-specified timepoints, each with associated 2-sided 95% confidence intervals.

Analyses will be performed using the ITT population as the primary efficacy analysis and PP population as supportive.

Sensitivity analyses maybe performed if deemed necessary.

8.2 Key Secondary Endpoint

ORR is defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) based on the independent radiologic review and during the initial assigned study treatment. This analysis will be performed in the ITT population as the main analysis and the PP population as supportive analysis. To be assigned a status of a CR or PR, changes in tumor measurements must be confirmed by repeat assessments that must be performed at least 4 weeks (allowing a minus 3 day window) after the criteria for response are first met. This analysis will include assessments prior to an event or censoring under the primary PFS analysis. Patients with unknown or missing response will be categorized as non-responders and will be included in the denominator when calculating the proportion. An unstratified two-sided Fisher's Exact test at a 0.05 significance level will be used to investigate statistical differences between treatment groups.

A 95% Newcombe score confidence interval will be constructed for the treatment rate difference in ORR (Newcombe, 1998)

A sensitivity analysis will be performed for ORR without requiring confirmation of CR and PR.

8.3 Secondary Efficacy Analysis

8.3.1 Time to Progression

TTP (reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of first disease progression on initial treatment based on the independent radiologic review. Since dying without progression is a competing risk of progression, TTP is censored at death date for patients who died without disease progression. Additionally, in the following situations, PFS will be re-defined otherwise or censored:

- For patients who do not have evaluable radiologic assessment, TTP will be censored at randomization date (TTP=1 day) unless they die within 2 cycles of treatment (8 weeks plus 3 days allowing for a late radiologic assessment within the visit window).

If patients die within 2 cycles of treatment (8 weeks plus 3 days), TTP will be censored at death date

- For patients who only have none measurable lesion according to modified RECIST Version 1.1 (non-nodal lesions must be ≥1.0 cm in the long axis or ≥double the slide thickness in the long axis) within 21 days prior to the first dose of study treatment, TTP will be censored at the date of latest evaluable progression-free radiologic assessment or patients will be considered to have disease progression at the date of new lesion(s) or unequivocal progression in non-target disease
- For patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments than the study treatment before documented date of the first disease progression, TTP will be censored at the date of the latest evaluable progression-free radiologic assessment
- For patients who have not progressed, TTP will be censored at the time of the latest date of evaluable progression-free radiologic assessment if at most one missed/non-evaluable assessment prior to this assessment
- For patients who have first disease progression after two or more consecutive missed/non-evaluable scheduled or hypothetical assessments , TTP will be censored at the time of the evaluable radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable scheduled or hypothetical radiologic assessments
- For patients who have first disease progression documented between scheduled assessments, progression date is defined as the date of new lesion (if progression is due to new lesions) or defined as the earliest of the scan dates of the components that triggered the progression per independent radiologic review (if progression is due to increase in sum of measured lesions)

TTP will be analyzed in a similar fashion to PFS.

8.3.2 Overall Survival

Overall survival (OS, reported in weeks) is defined as the interval between the date of randomization and date of death from any cause. Patients who are still alive or who are lost to follow-up will be censored at the date of last contact. As mentioned in Section 3.1, OS will be analyzed during the entire study period in a similar fashion toPFS.

8.3.3 Time to Response

The time to response, based on the independent radiologic review, is defined as the interval between the date of randomization and the earliest date of first documented confirmed CR or earliest date of first documented confirmed PR if the patient does not have confirmed CR. Patients who do not have a confirmed PR or CR will be censored at the date of the last assessment during the double-blind treatment analysis period. Time to response will be summarized and displayed using KM methods in a manner similar to the primary analysis of PFS.

8.3.4 PFS Based on Investigator Assessment

As a sensitivity analysis to the primary efficacy analysis, PFS (reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of disease progression based on Investigator assessment or death on initial study treatment due

to any cause. In the situations mentioned in Section 8.1, PFS based on investigator assessment will be defined or censored in a manner analogous to which is used for PFS based on independent radiologic review.

PFS based on investigator assessment will be analyzed in similar fashion to PFS based on independent radiologic review.

8.3.5 Quality of Life

Quality of life (QOL) will be based on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaires.

The EORTC-QLQ-C30 will be summarized by scale. In all scales, a high scale score represents a higher response level. The scoring for this questionnaire will be done in 2 steps.

1. Calculate the average of the items that contribute to the scale. This will be used as the raw score for the scale, and
2. Apply a linear transformation to standardize the raw score, so that scores range from 0 to 100.

Changes from baseline to Day 1 of Cycle 2 in EORTC-QLQ-C30 Role function and Physical function will be compared between the two treatment arms using analysis of covariance (ANCOVA) model with the stratification factors as factors. If Day 1 of Cycle 2 value is missing, then the change from baseline to the end of initial study treatment will be used in the analysis.

The EQ-5D-5L is a standardized measure of health status comprised of a descriptive system including five health-related QOL states (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale (VAS) of overall health. Each dimension is rated on a 5-point response scale indicating severity of problems, where 1 is “no problems”, 2 “slight problems”, 3 “moderate problems”, 4 “severe problems”, and 5 is “extreme problems”. The five questions are scored and together contribute to the EQ-5D-5L index (utility) score between 0 and 1 (1 being perfect health), which will be calculated using the developers’ algorithm based on country-specific reference score sets (Van Hout et al., 2012). Score sets are available for Denmark, France, Germany, Japan, Netherlands, Spain, UK, US and Zimbabwe. For countries in which no score set exists (Canada, Hungary, Israel, Romania, and Sweden) the closest neighboring country will be used as a proxy (EuroQol Group, 2015), eg, UK value set for Australia, France value set for Belgium, USA value set for Canada and Singapore, and Germany value set for Poland. If scale is missing for one of the dimensions, the index (utility) score will have a missing value.

EQ-5D-5L will be summarized overall by number and percentage for each level of each dimension. For pain/discomfort and usual activities, the Cochran–Mantel–Haenszel test will be used to test the change in response scale at Day 1 of Cycle 2 from baseline between DCC-2618 and placebo. For EQ-5D-5L index (utility) score, an ANCOVA model with the stratification factors as factors will be used to compare the change at Day 1 of Cycle 2 from baseline between the two treatment arms.

The EuroQol visual analogue scale (EQ-VAS) is a measure of overall self-rated health status, used and analyzed separately from the index score. The EQ-VAS recorded the subject’s self-rated health on a 20 cm vertical VAS with endpoints labelled “the best health you can imagine” and “the worst health you can imagine.” The EQ-VAS score ranges from 0 to 100,

with higher scores indicative of better overall health. EQ-VAS will be summarized using continuous descriptive statistics. Change in EQ-VAS score at Day 1 of Cycle 2 from baseline between the two treatment arms will be tested with a t-test.

8.3.6 Disease Control Rate

Disease control rate (DCR) will be calculated and summarized with n and percentage. Disease control will be defined as having a response (complete or partial) or stable disease lasting at least 12 weeks. Other time points (6, 9, 12 months) may be added on an exploratory basis.

8.3.7 Duration of Response

Duration of response is defined as the time interval from the first assessment of confirmed CR or PR until the first disease progression or death. In the case that the PFS is censored, duration of response will be censored at the last evaluable progression-free radiologic assessment in an analogous manner.

Duration of response based on the independent radiologic review will be analyzed with Kaplan-Meier method using the 25th, 50th (median), and 75th percentiles and survival probability at pre-specified timepoints, each with associated 2-sided 95% confidence intervals. Duration of response based on the Investigator assessment will be analyzed in a similar fashion as well.

8.4 Handling of Missing Data

For the analysis of efficacy endpoints, handling of missing data has been specified in Sections 8.1, 8.2, and 8.3.

Algorithms for imputing partial or missing dates are shown below in Table 1. If a period determination cannot be made for an adverse event, it will be attributed to the randomized blinded period. AE end dates are imputed to facilitate calculation of AE duration.

Table 1 Imputation Rules for Partially Missing Dates

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event/Start Date	Assign first day of month unless it is the month of first dose of study medication. Otherwise, assign date of first dose of study medication or AE end date (if not missing) whichever is earlier	Assign January 1 unless the year is year of first dose of study medication Otherwise, assign date of first dose of study medication or AE end date (if not missing) whichever is earlier.	Assign date first dose of study medication.
Adverse Event End Date	Assign the last day of the month or death date or data cut-off date (or end of study date), whichever is earliest.	Assign December 31 or death date or data cut-off date (or end of study date), whichever is earliest.	If ongoing, end date is missing. Otherwise, assign death date or data cut-off date (or end of study date), whichever is earlier.

8.5 Multiple Comparisons/Multiplicity

To control familywise type-I error, the hypothesis tests for treatment difference between DCC-2618 and placebo will be performed at two-sided 0.05 level of significance sequentially in the following order:

1. The primary endpoint PFS based on independent radiologic review
2. The key secondary endpoint ORR based on independent radiologic review
3. OS
4. QOL as determined by changes from baseline to Day 1 of Cycle 2 in EORTC-QLQ-C30 Role function and Physical function (each at 0.025 level of significance)

If any hypothesis test is not significant at alpha=0.05 level, the subsequently listed analyses will be viewed as descriptive.

8.6 Examination of Subgroups

Subgroup analysis will be performed for the primary and key secondary efficacy endpoints defined by the following variables:

- Age (18 – 64 vs 65 – 74 vs 75 years or older)
- Gender (Male vs female)
- Race (White vs non-White vs not-reported)
- Region (US vs non-US)
- Screening ECOG (0 vs 1/2)
- Number of prior therapies (3 vs ≥4)

8.7 Interim Analysis and Data Monitoring

No interim analysis for efficacy will be performed for this study. An IDMC will be used to review safety data periodically throughout the course of this study.

The IDMC will consist of an experienced biostatistician and two qualified clinicians, who are not employees of the Sponsor, with combined scientific expertise in general oncology and GIST and practical experience conducting clinical studies and monitoring safety and efficacy of clinical studies. The IDMC or Sponsor may request an ad hoc meeting for any reason, including significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. The IDMC objectives and operational details will be defined in the IDMC Charter.

9 PHARMACOKINETICS

Individual patient's raw concentrations of DCC-2618 and actual sampling time will be listed by nominal sampling time point. Raw concentrations for each nominal sampling time point will be summarized with descriptive statistics such as number of subjects, geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, and geometric coefficient of variation, minimum and maximum.

10 SAFETY ANALYSIS

10.1 Study Drug Exposure

The duration of initial assigned study treatment in weeks, total dose, average daily dose, and relative dose intensity will be displayed using continuous descriptive statistics. In addition, the number and percent of patients in categories based on treatment duration and patients with dose increase, reduction, and interruption will be summarized.

The treatment duration will be calculated as (the date of last treatment before Open label or discontinuation treatment – date of first treatment of study drug + 1 day)/7. If the date of last treatment is missing because the true last treatment date is unknown or patients are still on treatment at the time of analysis, the earliest of the end of treatment (EOT) date, end of study date, death date, and data cut-off date will be used. The average daily dose will be calculated as the total dose received divided by treatment duration in days. The relative dose intensity (%) is the total dose received divided by the total planned dose and multiplied by 100%. These analyses will be performed for the Safety population.

10.2 Adverse Events

Adverse events tables will summarize the number and proportion of patients overall and by treatment arm with an event by each system organ class (SOC) and preferred term (PT) for the Safety population. All tables will only include treatment emergent adverse events (TEAEs), where TEAEs are defined as any AE that occurs that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug. In the case of missing start and/or stop date, non-missing date parts will be used to determine if an AE is treatment-emergent or not. An AE will be categorized as TEAE if a determination cannot be made using the non-missing date parts as to when the event occurred relative to study drug administration. Adverse event toxicity grade will be classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 criteria. For incidence summaries, a missing toxicity grade of a TEAE will be conservatively imputed as severe; for a TEAE missing causal relationship to study treatment, a causality of "related" will be assigned. Listings will include all reported AEs, flagging events that were TEAEs and displaying missing severity grades and causalities as they were entered in the clinical database.

An overall summary of the number of subjects with TEAEs as well as the number of event will be presented, including the number and percentage of subjects with any TEAEs, treatment-emergent serious adverse events (SAE), drug-related TEAEs and TEAEs leading to treatment discontinuation, study discontinuation, and death.

The number and percentage of patients reporting TEAEs, as well as the number of events, in each treatment group will be tabulated by SOC and PT; by SOC, PT, and maximum severity. If a patient has multiple occurrences of the same SOC and PT, then the patient will be counted only once for the SOC and PT using the most severe occurrence for the summarization by maximum severity. Presentation by SOC and PT will display SOC sorted alphabetically and PT by descending frequency within SOC.

TEAEs and drug-related TEAEs will be summarized by PT by descending frequency. Treatment-emergent SAEs, TEAEs leading to study treatment discontinuation and study discontinuation, and treatment-emergent SAEs leading to death will be summarized by SOC, PT, and treatment arm.

Adverse events of special interest (AESI) are serious or nonserious AEs of scientific and medical concern specific to study drug, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. AESIs will be flagged on the eCRF by the investigator. The following AEs are considered AESIs: squamous cell carcinoma of skin (SCC), actinic keratosis, and keratoacanthoma.

The number and percentage of patients by treatment arm with the following categories of TEAEs will be summarized in tables by SOC and PT:

- Any TEAE
- Any TEAE by toxicity grade
- Any TEAE Grade 3/4
- Any drug-related TEAE
- Any treatment-emergent SAE
- Any drug-related treatment-emergent SAE
- Any TEAE leading to dose modification(dose reduction or interruption)
- Any TEAE leading to treatment discontinuation
- Any TEAE leading to study discontinuation
- Any TEAE leading to death
- Any AESI
- Any AESI by toxicity grade
- Any AESI Grade ≥ 3
- Any drug-related AESI

10.3 Eastern Cooperative Oncology Group Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status Assessments will be summarized for each visit.

10.4 Clinical Laboratory Data

Clinical laboratory measurements will be collected from screening until the EOT visit (within 7 days of the last dose). Laboratory values will be graded for toxicity as defined by the NCI-CTCAE, Version 4.03 or higher.

Table 2. Safety Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
Glucose Blood urea nitrogen Creatinine Sodium Potassium Calcium Magnesium Phosphorus Total and direct bilirubin Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Lactate dehydrogenase Total protein Albumin Creatine Phosphokinase Globulin Triglycerides Lipase Amylase TSH T3 T4	Hemoglobin • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Mean corpuscular volume Hematocrit Platelets Leukocytes Reticulocytes Differential (absolute): • Eosinophils • Basophils • Neutrophils • Lymphocytes • Monocytes **Coagulation Studies (for patients taking anticoagulants)** • Activated partial thromboplastin time • Prothrombin time • International Normalized Ratio	Urine protein Urine blood Specific gravity Urine ketones Urine glucose

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change as well as shift in toxicity grade from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed.

Numeric laboratory values recorded as "<x" or ">x" will be handled as follows,

- In the listings, "<x" and ">x" will be presented as recorded
- In the summary tables of observed values and changes from the baseline and those for shifts in CTCAE grade, "<x" and ">x" will be converted to numeric values before the analysis,
  - "<x" will be converted to "x – 1e-6"
  - ">x" will be converted to "x + 1e-6"

In the summary tables of numeric values, the convention is to present 1 decimal place beyond those used in raw data for median and mean and 2 more decimal places beyond those used in

raw data for standard deviation and standard error. There will be no deviation from this convention to display 6 or more decimals due to any conversion using the above rules.

10.5 Vital Signs

Summary and change from baseline for weight, temperature, heart rate, respiratory rate, and blood pressure will be summarized overall by time point utilizing continuous descriptive statistics.

10.6 Electrocardiograms

PR, QRS, QT, QTc (ie, QTcB and QTcF) and RR intervals and their change from baseline will be summarized for each treatment group by scheduled visit. Patients will be categorized into > 450, > 480, and > 500 ms per their maximum post-baseline absolute QTc interval and > 30 and > 60 ms per their maximum change from baseline QTc interval. Additionally, patients will be classified into the following categories: HR ≤50 bpm and/or decrease from baseline ≥20 bpm; HR ≥120 bpm and/or increase from baseline ≥20 bpm; PR ≥220 ms and/or increase from baseline ≥20 ms. The number and percentage of subjects in each category will be summarized for each treatment group.

10.7 Echocardiograms/Multigated Acquisition Scans

Summary and change from baseline for left ventricular ejection fraction (LVEF) will be summarized overall by time point utilizing descriptive statistics. Change from baseline in LVEF will be summarized with number and percentage of patients who have a >20% absolute decrease from baseline as well.

10.8 Dermatologic assessments

The number and percentage of subjects with new suspicious skin lesions will be summarized overall and by location.

10.9 Ophthalmologic assessments

The ophthalmologic assessments at baseline and any clinically indicated exams will be listed.

10.10 Prior and Concomitant Medications and Procedures

Prior medications and procedures taken or performed within 30 days prior to screening and prior to the first dose will be documented.

All concomitant medications and procedures (those taken or performed on or after the day of the first dose to 30 days after the last dose of study drug) will be documented.

Prior and concomitant medications will be summarized by the WHO Drug Dictionary Anatomical Therapeutic Chemical 2nd level (ATC-2) and preferred term (pharmacological subgroup ATC level 5), for the safety population. If the 2nd level term is not available, the next available level (eg, ATC-2) will be used.

The number and proportion of the patients who took each medication will be tabulated by the ATC-2 level and preferred name for concomitant medications. A patient will only be counted once within each ATC-2 code and within each preferred name.

All prior and concomitant medication data will be listed by patient.

11 STATISTICAL ANALYSIS DURING THE OPEN-LABEL ANALYSIS PERIOD

In general, the analysis methods and conventions specified in Section 3.2 to 10.10 will be applied to the open-label analysis period, with exceptions described as below.

11.1 Analysis Sub-periods

The open-label analysis period will be further split into 2 sub-periods:

- Prior to intra-patient dose escalation
- Post intra-patient dose escalation

Days on DCC-2618 treatment within the open-label analysis period for patients that crossed over to DCC-2618 will be defined from the first dose date after crossover.

11.2 Baseline

During the open-label analysis period, Study Day will be calculated using the same reference start date as defined in Section 3.3.

For the "Prior to intra-patient dose escalation" sub-period, baseline will be defined as the last non-missing value prior to the first administration of DCC-2618 150mg QD.

For the "Post intra-patient dose escalation" sub-period, baseline will be defined as the last non-missing value prior to the first administration of DCC-2618 150mg BID.

11.3 Analysis Populations

For the "Prior to intra-patient dose escalation" sub-period, the analysis population will be the safety population, including patients who have been treated with DCC-2618 but not yet at 150mg BID in the open-label period.

For the "Post intra-patient dose escalation" sub-period, the analysis population will be the safety population, consisting of patients who have been treated with DCC-2618 at 150mg BID in the open-label period.

For each sub-period, the PK population will include patients who received at least 1 dose of DCC-2618 at 150mg QD or 150mg BID and had at least 1 non-missing PK concentration in plasma reported for DCC-2618.

ITT and PP populations are not applicable to the open-label analysis period.

11.4 Efficacy Analysis

Efficacy analysis during the open-label analysis period will be explored by analysis sub-periods.

For patients who initially received placebo and subsequently crossed over to DCC-2618 treatment, PFS in the "Prior to intra-patient dose escalation" sub-period will be defined as the time interval from the date of the first dose of DCC-2618 to the earliest documented evidence of disease progression. PFS will be re-defined or censored as needed, and analyzed in a similar fashion to the primary efficacy endpoint.

For patients in the "Intra-patient dose escalation" sub-period, efficacy assessment data will be presented in listings only.

11.5 Safety Analysis

Exposure to DCC-2618 will be summarized by analysis sub-periods. The duration of DCC-2618 in weeks, total dose, average daily dose, and relaive dose intensity will be displayed using continuous descriptive statistics. In addition, the number and percent of patients in categories by treatment duration and patients with a dose increase, reduction, and interruption will be summarized.

All the AEs and the other safety data collected during the open-label analysis period will be analyzed. All the AEs in the open-label analysis period will be analyzed as TEAEs.

TEAEs and the other safety endpoints will be analyzed by treatment groups as defined by patients' initial treatment in the double-blind treatment period, for all patients who entered in the open-label analysis period overall and separately for each sub-period.

12 QUALITY CONTROL

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).

The sponsor will review all tables, listings, and figures prior to final database lock. Final SAS datasets, programs and outputs will be transferred to the sponsor at project completion.

13 REFERENCES

Newcombe, R. G. 1998. Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods. Statistics in Medicine, 17, pp. 873-890.