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Statistical Analysis Plan Amendment 1

Title: A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome

Protocol Number: MK-7075-002/ARQ 092-103

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Version	Issue Date	Section	Revision/Addition	Rationale
2.0	*xxMay2022*	4.6	A listing of participants by Investigator name and treatment group was added.	Added per Sponsor's request.

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1 INTRODUCTION

This document details the planned statistical analyses for the ArQule, Inc., (a wholly owned subsidiary of Merck Sharp and Dohme, a subsidiary of Merck & Co., Inc.), protocol "MK-7075-002/ARQ 092-103" study titled "A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome".

2 STUDY DESIGN

This is an open label, multi-center Phase 1/2 study of oral miransertib administered daily to patients with phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA)-related Overgrowth Spectrum (PROS) and Proteus Syndrome (PS). This is a two-part study (Part A and Part B) that will be conducted at approximately 20 sites globally.

Part A includes all participants enrolled in the study prior to Protocol Amendment 6. Part A was designed to enroll 25 to 40 participants with PROS and PS. These participants will continue treatment according to the schedule of drug administration/assessments they have been on at the time of the amendment 6 approval.

Part B includes all participants enrolled under Protocol Amendment 6 or higher. Part B will enroll approximately 65 participants with clinical diagnosis of PROS or PS with documented somatic PIK3CA or v-Akt murine thymoma viral oncogene homolog (AKT1) mutations. Part B is comprised of four cohorts.

- Cohort 1 will enroll 20 participants with PROS with a measurable lesion by the study-standardized volumetric magnetic resonance imaging (MRI).
- Cohort 2 will enroll 10 participants with PS with measurable cerebriform connective tissue nevus (CCTN) and pre-CCTN lesional area by the study-standardized photography.
- Cohort 3 will enroll approximately 25 PROS or PS patients who do not meet the eligibility criteria for enrollment in Cohort 1 or Cohort 2.
- Cohort 4 will enroll participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access.

Cohorts 1 and 2 were originally designed to determine the response rate of miransertib in a selected participant population, as measured by a change in target lesion size from baseline, using blinded independent central imaging review: volumetric MRI in PROS or cerebriform connective tissue nevus (CCTN) photography in PS.

In Part B (except Cohort 4), participants will receive miransertib at the 15 mg/m^2 qd dose level during the first 3 cycles (a cycle of therapy is considered to 28 days). The dose will be increased to 25 mg/m^2 qd provided no clinically significant drug-related toxicity is observed. Participants who experienced miransertib-related toxicity or are unable to tolerate study medication during the first 3 cycles may be treated at lower doses.

Participants enrolled in Cohort 4 will continue treatment at the dose they were on at the time of enrollment, but their dose should not exceed the 25 mg/m^2.

Participants will stay on treatment for up to 48 cycles.

The study data and endpoints underwent an internal review by the Sponsor in 2020. It was concluded that the current data from this study would not be sufficient to establish efficacy for either the PROS or PS patients. As a consequence, Protocol Amendment 7 was written to remove all efficacy assessments, including the volumetric MRIs for the PROS patients, the CCTN photography for the PS patients, as well as to remove the functional assessments, among others.

2.1 Study objectives

2.1.1 Primary Objective

The primary study objective for both Part A and Part B is to describe the safety and tolerability of miransertib in patients with PROS and PS.

2.2 Endpoints

2.2.1 Part A and Part B Endpoints

Under Protocol Amendment 7, the endpoints for Part A and Part B have been combined to assess the safety and tolerability of miransertib in participants with PROS and PS based on the frequency, duration, and severity of AEs from the first dose of the drug through 90 days after the last dose of the drug.

2.3 Sample size

Part A:

Enrollment in Part A was stopped upon approval of Protocol Amendment 6. 25 to 40 participants were planned to be enrolled.

Part B: Cohorts 1 and 2

Part B of this study was originally designed to determine the efficacy in PROS and PS patients treated with a daily dose of miransertib. The primary endpoint for Cohort 1 and Cohort 2 was response rate as assessed by blinded reviewers (with adjudication) using protocol response criteria. The sample size was justified based on the precision of a 95% confidence interval (CI) on the response rate. To exclude a clinically irrelevant response rate of 5%, the lower limit of the 95% CI should be higher than 5%.

- Cohort 1, PROS: A sample size of n=20 participants will provide a two-sided exact Clopper-Pearson 95% CI of (6%, 44%) on an observed response rate of 30%.
- Cohort 2, PS: A sample size of n=10 participants will provide a two-sided exact Clopper-Pearson 95% CI of (7%, 65%) on an observed response rate of 30%.

With Protocol Amendment 7, efficacy assessments will no longer be collected, and the primary objective of the study is the evaluation of safety and tolerability of miransertib.

Part B: Cohorts 3 and 4

Approximately 25 and 10 patients will be enrolled in Cohorts 3 and 4, respectively.

3 RANDOMIZATION

This is an open label study, with all participants receiving miransertib, so randomization is not applicable.

4 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

4.1 Analysis Sets

Participants excluded from the analysis sets and the reason for their exclusion will be listed.

4.1.1 Screened Population

The Screened Population includes all participants who were screened and who signed informed consent.

4.1.2 Safety Population

The Safety Population includes all participants who received at least one dose of study medication.

4.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

4.2.1 Race

Where more than one race category has been selected for a participant, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

4.2.2 Baseline

Unless otherwise defined, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of miransertib.

4.2.3 Duration/Study day/Time

Study day will be calculated as the number of days from first dose of miransertib.

- date of event – date of first dose of miransertib + 1, for events on or after first dose
- date of event – date of first dose of miransertib, for events before first dose.

4.3 Conventions for Missing and Partial Dates

All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual participant listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

4.3.1 Missing/Partial Start/Stop Date of Adverse Events and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved or the participant has stopped taking the concomitant medication, the stop date will be imputed as the date of the participant's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the participant's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the participant's last clinic visit in which case the date of participant's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.

- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the participant's screening date or the stop date of the event/concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

4.3.2 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date when the participant would have run out of study drug assuming full compliance from the date the study drug was last dispensed or the date of participant's last clinic visit in the study or early withdrawal or death whichever the earlier.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the participant would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of participant's last clinic visit in the study or early withdrawal or death whichever the earlier.

4.3.3 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

4.3.4 Exposure to Study Drug

Exposure to miransertib will be calculated as follows: date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

4.3.5 Inexact Values

In the case where a laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

4.3.6 Electrocardiogram Data

For electrocardiogram (ECG) data recorded on continuous scales, if more than one value is recorded at a time point, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

4.3.7 Unscheduled Visits

Only scheduled post-baseline laboratory, vital signs, and ECG values will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

4.4 Conventions

All data listings, summaries, and figures will be generated using SAS version 9.4 or higher[1].

Summaries will be presented by Part (A/B), Cohort (and by dose within Cohort for adverse events [AEs]), and overall. Treatment group labels will be displayed as follows:

Part A	Part B				
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Overall

Listings will be sorted in the following order: Part, Cohort, participant ID, parameter, and cycle unless otherwise stated.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the participant population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

4.5 Decimal Places

Decimal places for derived data described in section 4.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

4.6 Disposition

Participant disposition will be summarized as follows:

- The number of participants included in the Screened Population and the Safety Population will be summarized by Part, Cohort and overall for the Screened Population.

- The number of participants who failed screening and the reasons for failure will be tabulated by Part, Cohort and overall for the Screened Population.
- The number of participants who completed the treatment period, completed the study, and who prematurely withdrew along with the reasons for withdrawal will be tabulated by Part, Cohort and overall for the Safety Population. Early withdrawals will also be summarized by the dose the participant was on at the time of withdrawal.
- The number of participants who completed each treatment cycle of the study will be summarized by Part, Cohort and overall for the Safety Population.
- A listing of participant disposition will be produced for the Enrolled Population.
- A listing of participants by Investigator name and treatment group will be produced for the Screened Population.

4.7 Protocol Deviations

Important protocol deviations and protocol deviations related to COVID-19 will be listed using the Safety Population.

4.8 Baseline Comparability

Demographics and baseline variables will be summarized by Part, Cohort and overall using the Safety Population.

The comparability of treatment Part and Cohorts with respect to participant demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

4.9 Demographics

The following baseline demographic variables will be summarized using standard continuous or categorical variable summaries: age at Informed Consent (years) both continuous and categorized as <18 years, ≥18 years), sex, race, ethnicity, height, weight, and body surface area (BSA). Additionally, a summary of participant characteristics for disclosure to public databases

(gender, race, ethnicity, age) will be produced for the Safety Population. The following age categories will be summarized:

- Newborns (0-27 days)
- Infants and toddlers (28 days – 23 months)
- Children (2-11 years)
- Adolescents (12-17 years)
- Adults (between 18 and 64 years)
- From 65 to 84 years
- 85 years and older

A listing of baseline demographic variables will be produced for the Safety Population.

4.10 **Medical History**

Previous and ongoing medical history conditions and previous surgical and medical procedures reported at screening will be presented together in a single table by Medical Dictionary of Regulated Activities (MedDRA) v24.0 primary System Organ Class (SOC) and Preferred Term (PT) and summarized by Part, Cohort and overall for the Safety Population. A listing of these data will also be produced.

Baseline disease characteristics related to PROS and PS (life stage overgrowth reported, any significant family history, disease diagnosis, and time since diagnosis [years]) will be summarized in a separate table and listing using the Safety Population.

The pathological diagnosis (genetic testing results) will be summarized in listing format only using the Safety Population.

A listing of all non-drug procedures related to PROS or PS will be produced using the Safety Population.

4.11 **Prior and Concomitant Medications**

Separate tabulations will be produced for prior and concomitant medications presented by Part, Cohort and overall for the Safety Population. Prior medications are defined as all medications

taken within 45 days of the first dose of miransertib. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, version B3 WHO Drug Global – March 2021, and will be summarized using ATC Level 2 and PT.
A listing of these data will also be produced.

4.12 **Exposure to Study Drug**

Duration of exposure is defined as the total number of days of study drug administration, ignoring any temporary drug interruption. Duration of exposure will be presented by Part, Cohort, and overall for the Safety Population.

Additionally, the total (cumulative) amount of administered treatment, dose intensity, and relative dose intensity will be summarized for the Safety Population. The amount of administered treatment will be calculated for each capsule strength as follows:

- Total amount of 5 mg dose received per cycle = 5 * [(total # of 5 mg capsules dispensed) - (total # of 5 mg capsules lost + total # of 5 mg capsules returned)
- Total amount of 10 mg dose received per cycle = 10 * [(total # of 10 mg capsules dispensed) - (total # of 10 mg capsules lost + total # of 10 mg capsules returned)

The total (cumulative) amount of administered treatment will be calculated as the sum of the total amount of 5 mg and 10 mg doses received across all cycles and for the entire study duration.

Relative dose intensity (expressed in mg/m^2) will be summarized using descriptive statistics and will present the number and percentage of participants receiving at least one dose at each level (i.e., 5 mg/m^2 daily, 10 mg/m^2 daily, etc.). Dose intensity (expressed in mg) is defined as the total dose received, calculated using relative dose intensity and BSA. Total dose received will be summarized using descriptive statistics.

Exposure data will also be listed using the Safety Population.

4.13 **Treatment Compliance**

A participant is considered compliant with the study protocol when study medication is administered at a compliance level of ≥80% (excluding dose holds for surgical operations or drug-related AEs). Treatment compliance will be calculated overall as follows:

(Total [cumulative] amount of treatment actually taken [mg])/Total [cumulative] amount of treatment that should have been taken [mg]) x 100

The total (cumulative) amount of treatment actually taken (mg) will be calculated as described in Section 4.12. The total (cumulative) amount of treatment that should have been taken (mg) will be calculated for each dose strength received as dose strength * (end date at that dose level – start date at that dose level) + 1 day, summed across all dosing records available for a participant.

Compliance will be summarized by Part, Cohort, and overall using the Safety Population. A listing of this data will also be provided.

4.14 **Pharmacokinetic Analyses (Part A and B)**

Pharmacokinetic analyses will be analyzed and reported in a separate report.

4.15 **Safety Analyses**

All participants who receive at least one dose of study treatment will be evaluated for safety.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, 12-lead electrocardiogram (ECGs), physical examination, vital signs, and clinical laboratory tests.

Descriptive summary statistics such as counts and percentages will be provided for safety analysis.

Exploratory analyses will also be performed on other safety parameters, as deemed appropriate,

within subgroups defined by age at enrollment (<12 years, ≥12 to <18 years, ≥18 years) and disease (PROS, PS). Further details regarding these subgroup analyses are provided in the following sections. ~~concomitant use of pain relief medications. Age subgroups to be considered will be less than 5, 5 to 7; 8 to 11; 12 to 18 subject to number of patients available within each of these~~

~~groups. Where an age group category has less than 5 patients then this category will be merged with the previous one.~~

4.16 **Adverse Events**

AEs will be assessed by the frequency, duration and severity from the first dose of miransertib through 90 days after the last dose of the drug. Severity of AEs will be assessed by the current version of Common Terminology Criteria for Adverse Events (CTCAE). A treatment emergent adverse event (TEAE) is defined as follows:

- Any AE that has an onset on or after the first dose of study drug and before last dose of study drug + 90 days.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug and before the last dose of study drug + 90 days.

A treatment-related AE (TRAE) is defined as an AE as being related to miransertib.

The following tables will be presented for AEs:

- Overall incidence and the number of TEAEs, ≥ grade 3 TEAEs, serious AEs (SAEs), TRAEs, serious TRAEs, TEAEs leading to early study withdrawal, and deaths (TEAEs leading to death and AEs leading to death).
- TEAEs by SOC and PT, incidence and number of events
- TRAEs by SOC and PT, incidence and number of events
- Serious TEAEs by SOC and PT, incidence and number of events
- Serious TRAEs by SOC and PT, incidence and number of events
- Serious TRAEs resulting in death by SOC and PT, incidence and number of events
- Serious non-TRAEs by SOC and PT, incidence and number of events
- Non-serious TEAEs by SOC and PT, incidence and number of events
- Non-serious TEAEs by SOC and PT, incidence >5% in one or more cohorts and number of events
- TEAEs by SOC, PT, and maximum toxicity, incidence
- TEAEs leading to early study withdrawal by SOC and PT, incidence
- TEAEs reported in ≥10% of participants by PT, sorted by decreasing incidence of PT

- TRAEs reported in ≥10% of participants by PT, sorted by decreasing incidence of PT
- Serious TEAEs reported in ≥5% of participants by PT, sorted by decreasing incidence of PT
- All AEs resulting in death by PT, sorted by decreasing incidence of PT
- Listing of TEAEs
- Listing of SAEs
- Listing of TEAEs leading to early study withdrawal
- Listing of subjects with TEAEs resulting in treatment interruption
- Listing of subjects with TEAEs resulting in treatment discontinuation
- Listing of AEs leading to death

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

Additionally, the following tables will be produced by grade (<3, ≥3) and separately by the subgroups of age at enrollment (<12 years, ≥12 to <18 years, ≥18 years) and disease (PROS, PS):

- TEAEs by SOC and PT, incidence and number of events
- TRAEs by SOC and PT, incidence and number of events; overall and separately by grade category (<3, ≥3)
- Serious TEAEs by SOC and PT, incidence and number of events; overall and separately by grade category (<3, ≥3)
- Serious TRAEs by SOC and PT, incidence and number of events; overall and separately by grade category (<3, ≥3)
- Serious non-TRAEs by SOC and PT, incidence and number of events; overall and separately by grade category (<3, ≥3)

TEAE duration by SOC and PT:

The duration of each AE for each participant will be calculated in days by subtracting the date of the start of the AE from the date of the end of the AE + 1 day. The AE duration will be summarized in the AE listings.

4.17 **Laboratory Data**

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by Part, Cohort, and treatment cycle for the following laboratory parameters:

- Hematology: complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell, platelet, and reticulocyte count
- Hemoglobin A1c (HbA1c)
- Coagulation tests (screening only): prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), D-dimer, and fibrinogen
- Blood chemistry: alkaline phosphatase, bicarbonate, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, and insulin
- Liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin, uric acid, total protein, and blood urea nitrogen (BUN)
- Electrolytes: sodium, potassium, and chloride
- Lipids: cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides

Each blood chemistry and liver function test parameter will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables from baseline to the minimum post-baseline value and separately to the maximum post-baseline value will be presented by Part, Cohort, and overall.

The incidence of post-baseline ALT, AST, ALP, and total bilirubin values meeting CTCAE criteria will be summarized by Part, Cohort, and overall. Refer to Appendix 1 of this SAP for CTCAE definitions for these parameters. Additionally, the incidence of participants meeting Hy's law criteria will be summarized. Hy's law criteria are defined as follows:

- ALT ≥5xULN or
- ALP ≥2xULN or
- ALT ≥3xULN and total bilirubin ≥2xULN

For the third criterion which requires both an elevated ALT and elevated total bilirubin value, both lab values must be elevated at the same visit in order to be counted.

The following laboratory parameters will be listed only:

- Serum pregnancy test for female patients of childbearing potential, if applicable
- Routine urinalysis: dipstick and microscopy including protein, glucose, and blood; pH, and specific gravity

A listing of all post-baseline clinically significant ALT, AST, ALP, or total bilirubin measurements, defined as measurements meeting ≥CTCAE grade 3 criteria, recorded throughout the treatment period will be presented.

4.18 Vital Signs

Vital signs will be collected at all treatment cycles. Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by Part, Cohort, overall and for each cycle:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiration rate (breaths/min)
- Body temperature (degrees Celsius)

4.19 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each follow-up:

- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTc interval (ms)

Additionally, the overall interpretation (Normal/Abnormal) and corresponding clinical significance for the interpretation will be summarized at each visit. All ECG data will be listed.

4.20 Physical Examination

All physical examination data will be listed.

5 INTERIM ANALYSIS

There will be no interim analysis for this study.

6 DATA MONITORING COMMITTEE ANALYSIS

The data monitoring committee (DMC) will monitor patients' safety by reviewing and evaluating study data, review study conduct and progress, and making recommendations concerning the continuation, modification, or termination of the study. DMC meetings will take place at least 2 times per year. There will be a formal charter outlining DMC membership and responsibilities.

A subset of the outputs defined as part of this SAP will form the DMC output reviewed at each DMC meeting.

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

General changes:
Under Protocol Amendment 7, the primary study objective for both Part A and Part B was updated to describe the safety and tolerability of miransertib in patients with PROS and PS, and further efficacy assessments were removed. Part A was closed to enrollment after the approval of Amendment 6. Amendment 7 will complete the final enrollment into the MOSAIC study and Compassionate Use/Expanded Access Program. In the future, patients will be transitioned to new miransertib programs.

Specific changes:
Protocol section 6.6 states that study drug compliance is to be calculated using the following formula:

- ([Number of capsules ingested] / [Number of capsules that should have been ingested])*100%.

Compliance is unable to be calculated using this formula. Subjects have the option of being administered capsules as either 5mg or 10mg, and it is not possible to determine from the data collected on the eCRF the actual number of capsules that should have been ingested. Because of this, an alternative method to calculate compliance has been specified in this SAP.

8 REFERENCES

1. SAS Institute Inc. The SAS System, Version 9.4. Cary, NC, SAS Institute Inc. 2014.

9 APPENDIX 1: CTCAE GRADES FOR SELECT LABORATORY PARAMETERS

Parameter	Unit	Definition	Grade 1	Grade 2	Grade 3	Grade 4
ALT	U/L	High	>ULN-3.0xULN if baseline was normal; 1.5-3.0x baseline if baseline was abnormal	>3.0-5.0x ULN if baseline was normal; >3.0-5.0x baseline if baseline was abnormal	>5.0-20.0xULN if baseline was normal; >5.0-20.0x baseline if baseline was abnormal	>20.0xULN if baseline was normal; >20.0x baseline if baseline was abnormal
AST	U/L	High	>ULN-3.0xULN if baseline was normal; 1.5-3.0x baseline if baseline was abnormal	>3.0-5.0xULN if baseline was normal; >3.0-5.0x baseline if baseline was abnormal	>5.0-20.0xULN if baseline was normal; >5.0-20.0x baseline if baseline was abnormal	>20.0xULN if baseline was normal; >20.0x baseline if baseline was abnormal
Alkaline phosphatase	U/L	High	>ULN-2.5xULN if baseline was normal; 2.0-2.5x baseline if baseline was abnormal	>2.5-5.0xULN if baseline was normal; >2.5-5.0x baseline if baseline was abnormal	>5.0-20.0xULN if baseline was normal; >5.0-20.0x baseline if baseline was abnormal	>20.0xULN if baseline was normal; >20.0x baseline if baseline was abnormal
Total bilirubin	mg/dL	High	>ULN-1.5xULN if baseline was normal; >1.0-1.5x baseline if	>1.5-3.0xULN if baseline was normal; >1.5-3.0x baseline if	>3.0-10.0xULN if baseline was normal; >3.0-10.0x	>10.0xULN if baseline was normal; >10.0x baseline if baseline was abnormal

Parameter	Unit	Definition	Grade 1	Grade 2	Grade 3	Grade 4
			baseline was abnormal	baseline was abnormal	baseline if baseline was abnormal	

ULN=Upper limit of normal
Values in table are based on CTCAE v5.0.