STATISTICAL ANALYSIS PLAN

Final Version 2.0, dated 17-June-2020

A Phase 1/2 Open-label Rollover Study for Subjects Who Have Participated in an Astellas Sponsored ASP2215 Trial

Protocol for Phase 1/2 Study of ASP2215

ISN: 2215-CL-0109

NCT02561455

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way
Northbrook, IL 60062

Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APGD	Astellas Pharma Global Development, Inc.
AST	Aspartate aminotransferase
CRF	Case report form
CTCAE	Common Terminology Criterion for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International normalization ratio
LA-CRF	Liver Abnormality-Case Report Form
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PD	Protocol deviation
PR	Partial remission
PT	Preferred term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings and figures
ULN	Upper limit of normal
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

List of Key Terms

Terms	Definition of Terms
Baseline	Observed values/findings which are regarded as the starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject and continues until the last assessment after completing administration of the test drug or comparative drug.
Screen failure	Potential subject who signed consent but did not meet 1 or more criteria required for participation in a trial and did not randomize to the trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the registration.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to database hard lock. This statistical analysis is coordinated by the responsible biostatistician of APGD. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and tables, listings and figures (TLFs) meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Assessments	**Screening** [a] (Day -28 to 1)	**Treatment Cycle 1 Day 1** [a]	**Day 1 of Treatment Cycle 3 and Every Other Cycle (i.e., Cycles 5, 7, 9, etc.)** [b] (+/- 5 days)	**End of Treatment** [c]
Informed Consent	X			
Verify Inclusion/Exclusion	X	X		
Subject Enrollment		X		
Demographics [d]		X		
Medical History [e]		X		
Physical Examination		X		X
Vital Signs		X		X
ECOG Performance Status		X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)		X	X	X
Pregnancy Test for Women of Childbearing Potential (WOCBP)		X	X	X
Prior and Concomitant Medications	←	—	—	→
Adverse Event Assessment [f]	←	—	—	→
ASP2215 Administration [g]		← Daily →		

ECOG: Eastern Cooperative Oncology Group

a. Subject should sign the informed consent at the final visit of the original study they enrolled in. The Screening and Treatment Cycle 1 Day 1 visits may be combined. A subject's procedures performed during their final visit for the original study will be used for Treatment Cycle 1 Day 1 if the final visit occurred within 7 days prior to visit.
b. Each treatment cycle is 28 days. Subject to be seen on Day 1 of every 2 treatment periods (every 8 weeks).
c. End of treatment visit to be conducted within 30 days of last dose, prior to starting a new anticancer therapy or upon marketing authorization and commercial availability of ASP2215 in the country of residence. Subjects discontinuing due to commercial availability will be notified by the site and an end of treatment visit scheduled within 3 months.
d. Demographic data will be obtained from the original study.
e. Medical history will be obtained from the original study.
f. Adverse events from the original study that are ongoing at the time of Screening will continue to be followed as adverse events during this protocol and should not be captured as medical history. Adverse events will be captured until the End of Treatment visit, 30 days after last dose, or until start of a new anticancer therapy, whichever is sooner.
g. Subject will continue dosing at the dose received in original study with ASP2215, dose not to exceed 280 mg. If the original subject dose is over 280 mg, the subject will begin dosing in this protocol at 280 mg.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

The objective of the study is to provide access to continued treatment for subjects who participated in other previous Astellas sponsored ASP2215 (single agent) trials and for whom the Investigator feels the subject may benefit from continued treatment.

3.2 Study Design

This is a multi-center, open-label, rollover protocol for Astellas sponsored, single agent ASP2215 trials in Acute myeloid leukemia (AML) and advanced solid tumors. Subjects must have completed the protocol requirements of the previous ASP2215 trial and be actively participating in the previous ASP2215 trial. In addition, subjects must be continuing to derive clinical benefit from treatment with ASP2215 without any persistent intolerable toxicity from ASP2215, in the opinion of the investigator and must meet the entry criteria for this rollover study prior to being enrolled.

Subjects should sign the informed consent at their cycle 1 day 1 visit. The assessments from the last treatment visit from the parent study can be utilized for the cycle 1 day 1 visit. The subject will then receive ASP2215 study drug for the rollover study and return all ASP2215 study drug from the parent study.

The number of subjects and number of centers will be dependent on the number of subjects and centers that enroll into the protocols rolling over into this trial. Centers in North America, Europe and Asia may rollover subjects into this trial. It is estimated that up to approximately 130 subjects across 40 centers will enroll into this trial. Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined in the protocol or upon marketing authorization and commercial availability of ASP2215 in the country of residence.

Subjects will continue ASP2215 at the dose they were on at the time of their end of study visit in the previous ASP2215 study.

3.3 Randomization

There was no randomization necessary.

4 SAMPLE SIZE

The sample size for this study is based on the number of subjects who are continuing to derive benefit from treatment with ASP2215 as assessed by their Investigator at the completion of the original study they enrolled under.

5 ANALYSIS SETS

In accordance with International Conference on Harmonisation (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

5.1 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all enrolled subjects who received at least one dose of study medication (ASP2215) and will be used for safety analyses.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

Not applicable.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs); frequency, severity, seriousness, and relationship to study drug.
- Clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin, and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- Physical Examination
- ECOG Performance Scores

All adverse events (AEs) recorded on treatment including within 30 days from the last study treatment or until start of a new anticancer therapy, whichever is sooner will be summarized. AEs will be coded to System Organ Class (SOC) and Preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 and will be graded according to the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. The adverse events recorded prior to the first dose of study medication will be considered as adverse events during the pre-investigational period.

TEAE is defined as an adverse event observed after starting administration of the test drug/comparative drug within 109 study. If the adverse event occurs on Day 1 and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAE. The ongoing adverse event from original protocol will not be considered as TEAE of this study.

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

6.3 Pharmacokinetic Variables

There were no pharmacokinetic variables in this study.

6.4 Pharmacodynamic Variables

There were no pharmacodynamic variables in this study.

6.5 Other Variables

- The duration of exposure

  For each subject, the Length of Time on treatment will be calculated in days, using the following formula:
  Date of last dose of study drug – Date of first dose + 1 – number of days without drug administration in between
  When the start or stop date is missing, then the exposure will be treated as missing.

  Percent overall compliance

  Treatment compliance is defined as the total number of study drug actually taken by the subject divided by the number of study drug expected to be taken during the study multiplied by 100.
  Total number of study drug actually taken is calculated as total number of tablets dispensed – total number of tablets returned
  Number of study drug expected to be taken is calculated as (Date of last dose of study drug – Date of first dose + 1) x planned number of tablets per day (see table below)

Daily Dose (mg)	Number of Tablets per Day
40	1
80	2
120	3
200	5
280	7

  When the total number of tablets taken is missing, then the compliance will be treated as missing.

- Previous and concomitant medication

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) will be mentioned in the relevant section.

Safety analysis and other summaries based on SAF will be presented by actual treatment received. Baseline refers to Cycle 1 Day 1. If no data was collected on Cycle 1 Day 1 the last value or measurement taken prior to study drug administration will be utilized as baseline.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest please refer to section 7.8.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued before study enrollment, registered by treatment arm;
- Number and percentage of subjects completed and discontinued screening, treatment, or study by primary reason for treatment discontinuation for all dosed subjects by treatment arm;

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all dosed patients. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics.

Number and percentage of subjects in each country and site will be presented by treatment group for the SAF.

Descriptive statistics for age, height, weight and BMI at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (<65 years vs. >= 65 years) and race will be presented. This will be done for the SAF.

Medical history is coded in MedDRA and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group for the SAF.

Disease history will not be summarized. Each subject's complete cancer history will be listed.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with World Health Organization – Drug Dictionary (WHO-DD), and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the SAF.

As with previous medication, concomitant medication will be summarized for each treatment group by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

7.2.5 Non-Medication Therapy

Frequency tabulations of subjects with non-medication therapy and reason for use will be presented by treatment group for SAF. Number of non-medication therapy received per subject will be summarized using descriptive statistics.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for the SAF:

- Number and percent of subject with dose increases, decreases or interruptions by treatment group.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented by treatment group.
- Exposure time will be categorized according to the following categories by treatment group:
  - less than 7 days
  - at least 7 days, less than 14 days
  - at least 14 days, less than 28 days
  - at least 28 days, less than 42 days
  - at least 42 days, less than 84 days
  - 84 days or more
  - Unknown.

Counts and percentages of subjects in each of these categories will be summarized for each treatment group for the SAF.

7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
  - less than 50%
  - at least 50%, less or equal to 75%
  - greater than 75%, less or equal to 100%
  - greater than 100%
  - Unknown.

7.4 Analysis of Efficacy

Not Applicable.

7.5 Analysis of Safety

All analysis of safety will be presented by treatment group for SAF.

7.5.1 Adverse Events

All adverse events will be evaluated by incidence including serious adverse events (SAEs), deaths, and discontinuation due to adverse events. Severity, investigator-attributed relationship to study drug, duration, and outcome of the events will also be recorded. These adverse events will be coded by to SOC and PT using a MedDRA dictionary (v23.0) and will be graded by NCI-CTCAE Grade (v4.03).

An overview table by treatment group will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of drug related TEAEs leading to death
- Number and percentage of subjects with drug related TEAEs leading to death
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by treatment group. Summaries will be provided for:

- TEAEs
- Grade 3 or higher TEAEs
- Drug related TEAEs,
- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,

The number and percentage of subjects with TEAEs will be also summarized for:

- TEAEs by SOC, PT and relationship to study drug
- Serious TEAEs by SOC, PT and relationship to study drug
- TEAEs by SOC, PT and NCI CTCAE grade
- Serious TEAEs by SOC, PT and NCI CTCAE grade
- Drug related TEAEs by SOC, PT and NCI CTCAE grade
- TEAEs by PT only

In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing NCI-CTCAE grade or relationship to study drug, then the subject will be counted only once with the maximum NCI-CTCAE grade or relationship to study drug, however, if any of the grade or relationship are missing then the subject will be counted only once with missing value. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

If necessary, adverse events of special interest will be analyzed.

7.5.2 Clinical Laboratory Evaluation

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, coagulation and urinalysis based on local assessment will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the library reference ranges.

The number and percentage of subjects below and above reference range will be summarized for each treatment group at each visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented for each treatment group at each visit.

For hematology and biochemistry, shift tables will be presented:

- Shift tables of reference range changes from baseline to the worst finding during the treatment period (low, normal, high), and

- Summary shifts of reference range changes from baseline to the worst finding during the treatment period (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal or from normal to low]).

Laboratory results will also be graded using NCI-CTCAE v4.03, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different laboratory values meeting each criterion. For hematology and biochemistry NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects for each visit. Shift tables of NCI-CTCAE grade change from baseline to the worst post-baseline grade will also be presented.

Laboratory results will be used for summaries as described above.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria in liver function tests (LFTs) for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin (TBL), Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN
	> 5xULN
	> 8xULN
	> 10xULN
	> 20xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN

Parameter	Criteria
ALT or AST or Total Bilirubin(*)	ALT or AST > 3xULN (in subjects without liver metastases), > 5 x ULN (in subjects with liver metastases) or (Total bilirubin > 2xULN)
ALT or AST AND Total Bilirubin(*)	ALT or AST > 3xULN and Total bilirubin > 2xULN
ALT or AST AND INR(*)	ALT or AST > 3xULN and INR > 1.5xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzymes and total bilirubin during the investigational period will be presented by treatment group

7.5.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest value obtained during treatment for each subject for each treatment group.

The following potentially clinically significant criteria are defined for each parameter:

Vital Sign Variable	**Criteria**
SBP	≥180 mmHg AND ≥20 mmHg change from baseline
DBP	≥105 mmHg AND ≥15 mmHg change from baseline
Pulse Rate	≥120 bpm AND ≥15 bpm change from baseline

7.5.4 Electrocardiograms (ECGs)

Not applicable.

7.5.5 Pregnancies

A detailed listing of all pregnancies will be provided.

7.5.6 Ophthalmologic Assessment

A detailed listing of the Ophthalmologic variables for both eyes will be provided, if data are available.

7.5.7 Other Safety-Related Observations

- ECOG PS: A summary table by visit and grade will be produced. A detailed listing will be provided.

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Analysis of Pharmacodynamics

Not applicable.

7.8 Subgroups of Interest

No subgroup analysis is planned.

7.9 Other Analyses

No other analysis is planned.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned in this study. Clinical data might be reviewed on an ongoing basis.

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Refer to the specification document for TLFs in which more details are provided.

7.11.1 Missing Data

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

For continuous variables (e.g., clinical laboratory measurement, vital signs), subjects with missing baseline variable will be excluded from the analysis of change from baseline.

Missing end of treatment information will be imputed by last observation carried forward. Visit-by-visit analyses of data will exclude subjects who did not provide data at the visit in question.

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Visit Windows

Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule.

All the assessments will be allocated to case report form (CRF) or visit based on the table below:

CRF visit	**Visit Window**
Screening	Not applicable
Study Visit	C1D1 to Last Dose Date
End of Treatment Visit	Last dose date + 30

The value which assessment day is the closest to the defined target day within these windows is used. If two values are equally close, the latter is used in the analysis.

8 DOCUMENT REVISION HISTORY

Version	**Date**	**Changes**	**Comment/rationale for change**
1.00	19-NOV-2015	NA	Document finalized
2.00	17-JUN-2020	Many, abbreviations, dosing exposure, concomitant medications	Many discrepancies between protocol and SAP. Protocol amended.

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

10 APPENDICES

10.1 Appendix 1: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

PPD	PPD
Principal Biostatistician,	

Contributors and Reviewers

PPD	APGD
PPD	
PPD	GDO Management Global Data Science
PPD	

Author and Approver Signatories

(E-signatures are attached at end of document)

PPD was the study statistician for this study and the primary author of this Statistical Analysis Plan

PPD

PPD was the global statistical lead (STATL) for this project and biostatistics peer reviewer of this Statistical Analysis Plan

This Statistical Analysis Plan was approved by:

PPD

PPD