1.0   Title Page

Statistical Analysis Plan

Study M14-361

A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer (ED SCLC)

Date: 15 Nov 2018

Version 1.0

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3.0 Introduction

Veliparib is a novel small molecule and also a potent oral PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutic agents, including alkylating/methylation agents (TMZ, cyclophosphamide), crosslinking agents (cisplatin, carboplatin), platinum agents, topoisomerase inhibitors (irinotecan), and radiation. Nonclinical efficacy with veliparib in combination with these agents has been demonstrated across an array of tumor types, including melanoma, glioma, prostate, breast, and colon.

Preclinical studies data suggest the addition of veliparib to carboplatin would enhance the efficacy of carboplatin in several xenograft tumor models. In the BRCA1 deficient MX-1 model, veliparib administered at doses as low as 25 mg/kg/day significantly enhanced the efficacy of carboplatin. On the other hand, etoposide in combination with other approved chemotherapeutic agents is FDA approved as first-line treatment in subjects with SCLC. Carboplatin in combination with etoposide (both IV and oral formulations) has been extensively tested in randomized clinical trials in SCLC as well as in other tumor types.

Therefore, this study (Study M14-361) is being conducted to assess efficacy and toxicity of veliparib versus placebo in combination with carboplatin and etoposide in the treatment of subjects with ED SCLC who are previously untreated.

This SAP provides details to further elaborate statistical methods as outlined in Clinical Study Protocol M14-359 incorporating Amendments 1, 2, 3 and 4, and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

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4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of the study is to evaluate if the addition of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.

The secondary objectives of the study are to evaluate (1) if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved PFS versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC; (2) if veliparib in combination with carboplatin and etoposide results in improved objective response rate (ORR) versus placebo in combination with carboplatin and etoposide, at the time of completion of maintenance therapy, or completion of combination therapy if subject was not involved in maintenance phase. In protocol v.5 dated 22 NOV 2016, Chapter 4.0, objective response rate is to be evaluated by the combination therapy for all subjects. We modified the analysis period by adding maintenance phase following ITT (intent-to-treat) population principle to avoid observation bias; (3) if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy; (4) if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved OS versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy; (5) to further evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.

The tertiary objectives are to (1) evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide

followed by placebo monotherapy; (2) evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved DOR versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy; (3) compare PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by veliparib maintenance to PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by placebo maintenance; (4) evaluate ECOG performance status.

4.2   Design Diagram

This is a Phase 1 dose escalation and Phase 2 randomized double-blind study of veliparib in combination with carboplatin and etoposide and maintenance veliparib monotherapy. The veliparib dose and schedule for the Phase 2 was determined to be 240 mg BID (twice a day) on a 14-day schedule for up to 6 cycles (21 days per cycle) based on the analysis of Phase 1 data. This SAP is only for Phase II part of the study. Analysis for Phase I part will be presented in CSR Phase I portion and when the study is complete PK analysis will be drafted in Appendix 16.1__9.1.

Approximately 180 adult male or female subjects with treatment-naïve ED SCLC will be selected to participate in the study to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Subjects will be randomized in a 1:1:1 ratio to one of three treatment arms:

Arm A: veliparib 240 mg BID in combination with carboplatin/etoposide for up to 6 cycles followed by veliparib 400 mg BID monotherapy;

Arm B: veliparib 240 mg BID in combination with carboplatin/etoposide for up to 6 cycles followed by placebo monotherapy;

Arm C: placebo in combination with carboplatin/etoposide for up to 6 cycles followed by placebo monotherapy;

Subject randomization for Phase 2 will be stratified by gender and baseline lactate dehydrogenase (LDH) level, that is, > Upper Limit of Normal (ULN) versus ≤ ULN. The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

The detailed dosing schedules for these three groups of the study are presented below in Table 1.

Table 1.   **Treatment Schema for Combination Cycles in Phase 2**

Days	–2	–1	1	2	3	4 - 12
Veliparib/Placebo	240 mg BID	240 mg BID	240 mg BID	240 mg BID	240 mg BID	240 mg BID
Carboplatin			Once			
Etoposide			Once	Once	Once	

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued combination treatment and/or if local SOC guidelines require 6 cycles of platinum-based therapy. Subjects enrolled in these additional 2 cycles of combination therapy will receive veliparib at 400 mg BID continuous dosing (21-day cycles) (Arms A), or matching placebo (Arms B and C) as per treatment arm assignment, until disease progression (PD) or unacceptable adverse events (AEs) occur.

All subjects will remain on study until reaching a protocol-defined event of PD or AE due to veliparib or carboplatin/etoposide. Otherwise, appropriate dose modifications or dosing delays should be managed according to protocol. Subsequent cycles of therapy will be administered if there is no evidence of PD and observed toxicities have recovered adequately as described in protocol.

4.3   Sample Size

Assuming a median PFS of 5.5 months for placebo in combination with carboplatin and etoposide followed by placebo monotherapy (Arm C) and a hazard ratio of 0.63 for veliparib in combination with carboplatin and etoposide followed by veliparib monotherapy (Arm A) versus Arm C, a total of 85 PFS events will provide an least 80% power to detect a statistically significant difference between Arm A and Arm C at a one-sided $\alpha = 0.1$.

Further assuming a hazard ratio of 0.75 for veliparib in combination with carboplatin and etoposide followed by placebo monotherapy (Arm B) versus Arm C, a total of 126 PFS events will be observed across all three arms at the time when 85 PFS events are observed for Arm A and Arm C combined. A total of approximately 180 subjects (60 subjects per treatment arm) will be enrolled into the study to obtain the 126 PFS events.

4.4   Interim Analysis

A safety DMC (Data Monitoring Committee) was set up for the Phase 2 portion of the study to review the aggregate unblinded safety data. The initial safety DMC review will occur once at least 30 Phase 2 subjects have met criterion 1) and 2), or 3), or 4).

1). Received at least one dose of veliparib/placebo;

2). Started Cycle 5; or

3). Discontinued (not death) prior to Cycle 5 due to AE not related disease progression; or

4). Death prior to Cycle 5 not due to disease progression.

Data cutoff date was Aug. 25th, 2017 and the safety DMC meeting was held on Oct. 18th, 2017. Based on this initial safety DMC review, it's decided that it's not necessary to have another safety review before DB lock. The details of the safety DMC setup and procedure was outlined in Appendix 14.1.7.

5.0　　Analysis Populations

5.1　　Definition for Analysis Population

Two study populations will be analyzed, respectively defined as follows:

Intent-To-Treat (ITT) population – all subjects who were randomized using an IRT (interactive response technology) system. The data from ITT population will be analyzed by the treatment group assignment given at the time of randomization, even if the subject takes the incorrect drugs that do not match the assigned treatment, or does not receive any treatment, or does not follow the protocol until completion.

As-Treated (AST) population – all subjects who were randomized by IRT system and took at least 1 dose of study drug (veliparib/placebo). The data from AST population will be analyzed by the actual treatment that subject received.

5.2　　Variables Used for Stratification of Randomization

Subject randomization were stratified by LDH level ($>$ ULN versus $\leq$ ULN), and gender (female versus male).

6.0　　Analysis Conventions

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a one-sided P value ≤ 0.1 (when rounded to one decimal place). The date of randomization is defined as the date that the IRT issued a subject number.

Unless otherwise specified, demographic and baseline characteristics, medical history, prior oncological therapies, and other medications, as well as all efficacy analyses will be performed on Phase 2 ITT population, and all safety analyses will be performed on Phase 2 AST population. Summary data will be presented for each of the three treatment arms (A, B, C), or as indicated otherwise.

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to veliparib/placebo, and carboplatin/etoposide. The first dose date of study drug for combination period is defined as the date of the 1st dose of veliparib/placebo or carboplatin/etoposide received during combination period, whichever occurs first. The last dose date of study drug for combination period is defined as the date of the last dose of veliparib/placebo or carboplatin/etoposide received during combination period, whichever occurs later. The first dose date of study drug for maintenance period is defined as the date of the 1st dose of veliparib/placebo received during maintenance period. The last dose date of study drug for maintenance period is defined as the date of the last dose of veliparib/placebo received during maintenance period.

Definition of Post-Treatment Therapy

Unless otherwise specified, the post-treatment therapy (excluding surgical and radiation therapy) in this document refers to the therapy after the last dose of study drug.

Stratification Factor for Efficacy Analyses

Baseline LDH ($\leq$ ULN versus > ULN) will be used in all stratified analyses of the efficacy endpoints. The stratification factor value under which the subject is randomized by the IRT will be used in the efficacy analyses.

Dealing with Multiple Values on the Same Day

If multiple lab values on the same day are available for a post-baseline measurement, then the value with the highest NCI CTCAE grade (or worst scenario) will be used in the assessment of shift from baseline to post-baseline. Arithmetic averages will be taken for the mean change analyses in lab values and vital signs values.

Definition of Baseline

All baseline summary statistics and analyses will be based on baseline for each variable. Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained on or prior to the date of first dose of study drug (or randomization date for untreated subjects).

Unless otherwise specified, baseline in rest of the document refers to the Baseline defined here.

Definition of Final Value

For ECOG, laboratory and vital signs variables, final value is defined as the last non-missing observation collected after the first dose of study drug in combination period to the 30 days after the last dose of study drug in combination period, or the last dose of veliparib/placebo in maintenance period if subject received any maintenance monotherapy.

Unless otherwise specified, final value in rest of the document refers to the Final Value defined here.

Definition of Analysis Windows

All time points and corresponding time windows are defined for each cycle are based on Cycle Rx Day 1 of each cycle.

Visit-wise longitudinal analyses such as change from baseline to all post-baseline assessments will be performed for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day.

The time windows specified in Table 2 describe how the data will be assigned to the protocol specified visits. Analysis time windows are constructed using the following algorithm:

- Determine the nominal Cycle Rx Day for each scheduled visit.
- Determine the window around a specific nominal Cycle Rx Day as in Table 2.
- If more than one assessment is included in a time window, the assessment closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

Table 2.   **Time Windows for ECOG performance status**

Scheduled Visit	Nominal Cycle Rx Day	Time Window (Cycle Rx Day Range)
Baseline	Baseline	Per baseline definition
Combination Cycle X Day 1	Rx day of Combination Cycle X Day 1	[−5, 1]
Combination Cycle X Day 8*	Rx day of Combination Cycle X Day 8	[−3, +3]
Maintenance Cycle XX Day 1	Rx day of Maintenance Cycle 1 Day 1	[−5, +5]
Final Value	NA	From baseline to final value per definition

Note: X refers to 2, 3, 4 … XX refers to 1, 2, 3, 4 …

7.0   Demographic and baseline characteristics, medical history, prior oncological therapies, and concomitant medications

7.1   Demographic and Baseline Characteristics

Categorical demographic and baseline characteristic variables will be summarized with the number and percentage of subjects, including those with missing information. Continuous demographic and baseline variables will be summarized with summary

statistics (mean, standard deviation, median, minimum and maximum). There will be no statistical comparison for demographic and baseline characteristics.

Continuous demographic variables include age, baseline height, weight. Categorical demographic variables include gender (male, female) and race (White, Black, Asian, American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander).

Continuous baseline characteristics include baseline tumor burden (based on the sum of baseline target lesion sizes (mm)), and number of baseline lesion sites (for one subject, one site counts as one regardless of the number of lesions that it carries).

Categorical baseline characteristics include baseline LDH value ($\leq$ ULN, > ULN), baseline ECOG performance (0, 1), medical/surgical history (yes, no), history of other cancer (yes, no), number of metastatic sites (0/1, $\geq$ 2), baseline diagnose stage M (M0, M1, unknown), tobacco use (former, current, never, unknown), and alcohol use (former, current, never, unknown).

7.2   Medical History

Medical history data will be summarized and presented using System Organ Class (SOC and Preferred Terms (PT)) according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The number and percentage of subjects with a particular PT will be summarized by alphabetical order of SOCs and alphabetical order of PTs within each SOC.

Subjects reporting more than one PTs within a SOC will be counted only once for that SOC. There will be no statistical comparison for medical history.

7.3   Prior oncological therapies, concomitant medications, and Post-Treatment Therapies

The number and percentage of subjects who took at least one dose of concomitant medication other than study drug, and subjects who received any post treatment therapy,

will be summarized separately by the generic medication name coded by WHO dictionary.

The number and percentage of subjects who have prior oncological therapies will be summarized by generic medication name and treatment setting (adjuvant, neo-adjuvant, metastatic). In addition, the best response of any therapies prior to study drug (or randomization for non-treated subjects) will be summarized.

There will be no statistical comparison for prior oncological therapies and other medications.

8.0   Subjects Disposition

Analyses for the subject disposition will be performed on ITT population. The screen failure reasons will be summarized for the screen failure subjects separately. The number and percentage of subjects will be summarized overall, by treatment arm, and by country for each of the following categories:

- Subjects who screen failed
- Subjects who were randomized into the study
- Subjects who never received any study drug
- Subjects who received randomized study drug
- Subjects who received study drug other than randomized
- Subjects who were in maintenance phase
- Subjects who discontinued study drug due to all reasons and primary reason
- Subjects who discontinued carboplatin due to all reasons and primary reason
- Subjects who discontinued etoposide due to all reasons and primary reason
- Subjects who discontinued maintenance veliparib/placebo due to all reasons and primary reason
- Subjects who discontinued study due to all reasons and primary reason

9.0   Study Drug Exposure

Analyses for the study drug exposure will be performed on AST population. Some definitions are provided as follows.

1. Combination therapy period

The following calculations only include data prior to maintenance monotherapy.

   a. Total number of cycles a certain subject exposed to veliparib/placebo: total number of cycles during which subject received at least one dose of veliparib/placebo.

   b. Duration of veliparib/placebo of a certain subject: last dose date of veliparib/placebo of this subject minus the first dose date of veliparib/placebo of this subject plus 1.

   c. Total number of days a certain subject exposed to veliparib/placebo overall, and by cycle, respectively: total number of days this subject received veliparib/placebo (excluding days not on study drug) overall, and by cycle, respectively.

   d. Average daily dose of veliparib/placebo of a certain subject overall, and by cycle, respectively: total administered dose of veliparib/placebo of this subject divided by total number of days this subject exposed to veliparib/placebo overall, and by cycle, respectively.

   e. Dose intensity (DI) of veliparib/placebo of a certain subject is defined as the ratio of ATD (actual total dose) of veliparib/placebo of this subject and PTD (planned total dose) of veliparib/placebo of this subject, expressed as a percentage (%). ATD and PTD of veliparib/placebo will be defined in Table 3.

For carboplatin and etoposide, analysis of DI will be performed. Dose intensity (DI) of carboplatin/etoposide of a certain subject is defined as ratio of ATD of carboplatin/etoposide of this subject and PTD of carboplatin/etoposide of this subject,

expressed as a percentage (%). ATD and PTD of carboplatin/etoposide will be defined in Table 3.

Descriptive statistics (mean, standard deviation, median, and range) will be used to summarize total number of cycles, duration, and total number of days, average daily dose, and DI of veliparib/placebo in combination phase, and DI of carboplatin/etoposide in combination phase. The actual total dose (ATD), planned total dose (PTD), and dose intensity (DI) for veliparib/placebo, carboplatin and etoposide prior to maintenance monotherapy period are presented in Table 3.

Table 3. **Definition of Actual Total Dose, Planned Total Dose, And Dose Intensity for Study Drugs Prior To Maintenance Period**

	ATD (Actual Total Dose)	PTD (Planned Total Dose)	DI (Dose Intensity)
Veliparib/placebo	Actual total dose (mg)	480 mg* 14* (actual number of veliparib/placebo combination cycles −1) +480 mg* actual veliparib/placebo dosed days in the last combination cycle	100*ATD/PTD
Carboplatin	Actual total AUC (mg/mL/min)	5 mg/mL/min* actual number of chemo cycles	100*ATD/PTD
Etoposide	Actual total dose (mg/m^2)	3*100 mg/m^2* actual number of chemo cycles	100*ATD/PTD

Actual number of veliparib/placebo combination cycles refers to the number of cycles subjects are exposed to veliparib/placebo prior to the initiation of maintenance therapy (if any) as captured on drug administration pages in EDC.

Actual total dose of veliparib/placebo in combination cycles is calculated excluding premature veliparib/placebo doses, that being said, we exclude any veliparib/placebo dose that was administered 2 days (not necessarily continuous doses) before the start date of

carboplatin or etoposide in that cycle, whichever occurs first. If a subject received no carboplatin and etoposide in a cycle, which indicates a protocol deviation, then veliparib/placebo administered in this cycle will be excluded.

Actual number of chemo cycles refers to the number of cycles subjects exposed to carboplatin/etoposide as captured on drug administration pages in EDC.

2.   Maintenance monotherapy period

Duration, total number of days, average daily dose, and DI of veliparib/placebo as described above will be summarized by descriptive statistics for veliparib/placebo in maintenance monotherapy.

The actual total dose (ATD), planned total dose (PTD), and dose intensity (DI) for veliparib/placebo in the maintenance monotherapy period is presented in the Table 4.

Table 4.   Definition of Actual Total Dose, Planned Total Dose, And Dose Intensity for Veliparib/Placebo in Maintenance Period

	ATD (Actual Total Dose)	PTD (Planned Total Dose)	DI (Dose Intensity)
veliparib/placebo	Actual total dose (mg)	800 mg* duration of maintenance therapies	100*ATD/PTD

Duration of maintenance therapy is calculated by subtracting the start date of maintenance therapy from the end date of maintenance therapy plus 1.

3.   Dose reduction, delay, and interruption,

The numbers and percentages of subjects having dose reduction or interruption or delay for each study drug will be summarized for each treatment arm prior to maintenance monotherapy period. If a subject has any dose reduction from the previous dose of a certain drug, this subject will be considered as having experienced dose reduction of this drug. If the difference between the first dose dates of two adjacent cycles of a certain

drug is more than 21 days, the subject will be considered as having experienced a dose delay of this drug. If a subject skips one or more consecutive dosing days of any drug within a cycle, then this subject is considered as having dose interruption of this drug.

10.0   Efficacy Analysis

10.1   General considerations

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a one-sided P value ≤ 0.1 (when rounded to two decimal places). Confidence intervals will be two-sided 80% for all descriptive statistics. The date of randomization is defined as the date that the IRT issued a subject number.

The efficacy analyses will be performed on Phase 2 ITT population and presented by treatment arm. All randomized subjects will be included unless otherwise specified. The dosing schedules for each of the three arms are listed in detail in Section 4.2.

After observing 95 PFS events (75% of 126), a model-based prediction was performed to estimate the approximate date of the 126th PFS events across all 3 arms. The prediction estimated Sep. 14th, 2018 as the date of 126 PFS events across the three arms. Unless otherwise specified, Sep. 14th, 2018 will be the cutoff date for all efficacy analyses.

For all efficacy endpoints except OS, if a subject's blind has prematurely broken by sites before cutoff date, the date of premature blind break will be set as the cutoff date for that subject.

If a subject starts any systemic anti-cancer therapy post-discontinuation of study therapy, then PFS and DOR will be censored at last non-missing tumor assessment prior to the initiation date of the new systemic anti-cancer therapy; similarly ORR/DOR will be based only on tumor assessment prior to the initiation of any new systemic anti-cancer therapy.

10.2   Testing Hierarchy

This is a single primary efficacy endpoint (PFS, Arm A vs Arm C) study. Survival data (a total of approximately 136 death events targeted across all three treatment arms) will not be mature at the PFS primary analysis time, thus OS analysis at the time of PFS primary analysis will be considered as an interim analysis. If statistical test is significant (one-sided P value ≤ 0.1) for the primary efficacy endpoint, then the fixed sequence testing procedure will be performed with a significance level of 0.1 (one-sided) for key secondary efficacy endpoints sequentially. If primary PFS (Arm A vs. Arm C) is not significant, then statistical significance will not be declared for any of the secondary efficacy endpoints.

Hierarchical ranking and alpha spending for primary and each secondary endpoint at the time of PFS primary analysis and OS primary analysis is presented in Table 5.

Table 5.   Alpha-spending Boundary (One-sided p-value) for Each Ranked Endpoint

Endpoint	Timing	
	PFS Primary Analysis (approximately 126 PFS events across all 3 arms)	**OS Primary Analysis (approximately 136 deaths across all 3 arms)**
PFS (A vs C)	0.1	NA
OS (A vs C)	0.0001 (administrative purpose)	0.1
PFS (B vs C)*	0.1	
OS (B vs C)	0.0001 (administrative purpose)	0.1
ORR (A vs C)*	0.1	
ORR (B vs C)*	0.1	

(A, B, and C correspond to the three treatment arms, respectively.)

*   Analysis sets for these three tests are the same as PFS (A vs C).

10.3   Definition of Efficacy Endpoints

PFS (progression-free survival): the number of days from the date of randomization to the date of earliest radiographic disease progression or death provided no radiographic disease progression occurred.

All events of disease progression before the initiation of anti-cancer post-treatment therapy will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurs immediately after a subject misses two or more consecutive disease progression assessments (e.g., 84 days = 12 weeks if previous tumor scan were prior to or on Week 24 Day 7 (Day 168), 105 days = 15 weeks if previous tumor scan were in between of Week 25 Day 1 and Week 30 Day 7 (Day 210), and 126 days = 18 weeks if previous tumor scan were on or after Week 31 Day 1), then this subject's data will be censored at the last disease progression assessment prior to the missing disease progression assessments, or at randomization if disease progression occurred at the first post-baseline disease assessment. All events of death before the initiation of anti-cancer post-treatment therapy will be included for subjects (whether had post-baseline tumor assessment or not) who had not experienced disease progression, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Similar to disease progression, if a death event occurs immediately after a subject misses two or more consecutive disease progression assessments (length of gap is calculated the same way as disease progression), then this subject's data will be censored at the last tumor assessment before death, or at randomization provided subject did not have any post-baseline disease assessment.

If a subject did not have an event of disease progression nor has the subject died on or prior to the cutoff of PFS analysis, this subject's data will be censored at the date of his/her last disease assessment or randomization date provided subject did not have any post-baseline disease assessment.

OS (overall survival): the number of days from the date of randomization to the date of death. All events of death will be included.

If a subject did not die on or prior to the cutoff of OS analysis, this subject's data will be censored at the date of his/her last known alive date, which is defined as the last date of the last survival follow-up visit, the start date of the last AE, the start date or end date of the last dose of any study drugs, the last lab and vital sign collection date, or the last disease assessment date, whichever occurs the last.

ORR (objective response rate): the proportion of randomized subjects with objective response (confirmed) as assessed by the investigator using RECIST version 1.1. Response includes both CR (complete response) and PR (partial response). Confirmation is required to determine objective response. Confirmation rules are described as follows,

Confirmed CR: After the first tumor assessment showing CR, the CR will be considered confirmed if the very next tumor assessment also shows CR (with no other responses in between), and if the duration between the two CRs is greater than or equal to 28 days.

Confirmed PR: After first tumor assessment showing PR, the PR will be considered confirmed if a subsequent tumor assessment also shows CR/PR (irrespective of tumor assessment in between that show stable disease) and if the duration of the first PR and the next CR/PR is greater than or equal to 28 days.

All ITT subjects will be included in the ORR analysis. Subjects with no post-baseline confirmed response will be identified as non-responders. Data after the first appearance of PD, or the start date of any anti-cancer post-treatment therapy, whichever comes earlier, will not be included.

DOR (duration of overall response): the number of days from the date of the first confirmed response (CR or PR) to the earliest documentation of radiographic progressive disease or death. The inclusion and exclusion criteria for PD and death, as well as event censoring strategy, are the same as described in PFS endpoint.

If a subject is still responding on or prior to the cutoff of DOR analysis, then the subject's data will be censored at the date of the subject's last available disease assessment.

Subjects with no post-baseline confirmed response will not be included in the DOR analysis. Data after the first appearance of PD, or the start date of any anti-cancer post-treatment therapy, whichever comes earlier, will not be included.

10.4   Primary Efficacy Analysis

10.4.1   Progression-Free Survival (Arm A versus Arm C)

Time to PFS will be analyzed by Kaplan-Meier methodology and compared between Arm A and Arm C using a two-sided log-rank test stratified by LDH level. KM plots of these two treatment arms will be presented. Median PFS time and the corresponding 80% confidence interval will be calculated and constructed via Brookmeyer and Crowley (1982). A hazard ratio estimate of Arm A vs. Arm C and the corresponding 80% confidence interval will be obtained from a Cox proportional hazards model stratified by LDH level. In addition, progression free survival rates at Month 3 and 6 with their corresponding 80% CIs will also be provided using Kaplan-Meier estimation.

10.5   Secondary Efficacy Analyses

10.5.1   Progression-Free Survival (Arm B versus Arm C)

Time to PFS will be analyzed by Kaplan-Meier methodology and compared between Arm B and Arm C using a two-sided log-rank test stratified by LDH level. KM plots of these two treatment arms will be presented. Median PFS time and the corresponding 80% confidence interval will be calculated and constructed via Brookmeyer and Crowley (1982). A hazard ratio estimate of Arm B vs. C and the corresponding 80% confidence interval will be obtained from a Cox proportional hazards model stratified by LDH level.

10.5.2 Objective Response Rate (Arm A vs Arm C and Arm B vs Arm C)

The objective response rate and corresponding 80% confidence interval will be estimated and compared between Arm A and Arm C as well as between Arm B and Arm C, respectively, using a two-sided Cochran-Mantel-Haenszel test stratified by LDH level. In addition, waterfall plots depicting best percentage of change in each subject's sum of target lesion sizes will be displayed by each treatment arm.

10.5.3 Overall Survival (Arm A versus Arm C and Arm B versus Arm C)

OS will be analyzed by Kaplan-Meier methodology and compared between Arm A and Arm C as well as between Arm B and Arm C using a two-sided log-rank test stratified by LDH level. Median survival time for all three arms will be calculated and corresponding 80% confidence intervals will be presented. Hazard ratio estimates (Arm A versus Arm C, Arm B versus Arm C) and their corresponding 80% confidence intervals will be obtained from a Cox proportional hazards model stratified by LDH level.

10.6 Tertiary Efficacy Analyses

10.6.1 Duration of Overall Response

The distribution of DOR will be estimated for each treatment arm using Kaplan-Meier methodology. Median DOR will be estimated and an 80% confidence interval will be presented for each treatment arm.

10.6.2 Progression-Free Survival (Arm A versus Arm B)

A hazard ratio estimate of Arm A vs. Arm B and the corresponding 80% confidence interval will be obtained from a Cox proportional hazards model stratified by LDH level.

10.6.3 Overall Survival (Arm A versus Arm B)

Hazard ratio estimate of Arm A vs. Arm B for OS and the corresponding 80% confidence interval will be obtained from a Cox proportional hazards model stratified by LDH level.

10.6.4 ECOG Performance Status (Arm A vs Arm C and Arm B vs Arm C)

Mean Change (80% CI) from baseline to each scheduled post-baseline visit (as defined in Table 2) will be compared between Arm A and Arm C as well as between Arm B and Arm C using ANCOVA with treatment arm as a factor and baseline ECOG value as a covariate.

Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Post-baseline measurements will be excluded after 30 days of the last dose of veliparib/placebo (including both combination period and maintenance period), carboplatin, or etoposide, whichever occurs the last.

10.7 Efficacy Subgroup Analysis

To evaluate the impact of demographic and baseline characteristics on efficacy, subgroup analyses may be performed for OS and PFS between Arm A and Arm C, and presented in forest plots with hazard ratio estimate (80% CI) using Cox proportional hazard model for each subgroup. Subgroups defined below may be used for the subgroup analyses:

1. Schlafen-11 (SLFN11) expression (+, –) via IHC

2. LP-52 biomarker status (+, –) as determined by HTG technology

3. Gender (Male, Female)

4. Age (< 65 years, ≥ 65 years)

5. Region (US, EU, and the rest of world)

6. Baseline ECOG performance status (0, 1)

7. Smoking history (current smoker, never smoked, and past smoker as defined in Section 8.1.1.1 in protocol)

8. LDH ($>$ ULN, $\leq$ ULN) based on IVR for the stratification factor

9.   Four cross-over subgroups per gender and LDH categories (LDH > ULN in male, LDH > ULN in female, LDH ≤ ULN in male, LDH ≤ ULN in female)

10. Number of metastatic sites (1, ≥ 2)

10.8   Additional Efficacy Analysis

The following additional efficacy analysis may be performed:

1.   Modified PFS analysis for Arm A & Arm C to consider the initiation of any anti-cancer post-treatment therapy as an event.

2.   Modified ORR analysis for Arm A & Arm C and DOR analysis for all 3 arms where both confirmed and unconfirmed responses are to be considered.

11.0   Safety Analysis

11.1   General considerations

All safety analyses will be performed on Phase 2 AST population, and will be summarized by each treatment arm (A & B & C) for combination period alone. Safety analyses will include all data in the extracted database (no cutoff). For visit-wise safety analyses, the analysis visit widows as described in Table 2 will be used to align data. There will be no statistical comparison for safety analysis unless otherwise specified.

11.2   Analysis of Adverse Events

Analyses of adverse events will include only "treatment-emergent" events (TEAE), i.e., those that have an onset (worst CTC grade) prior to or on the 30 days of last dose of study drug in combination period. TEAEs will be coded and summarized by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary. Subjects reporting more than one AE will be counted only once in the overall analysis. Summary data by each treatment arm will be presented by but not limited to the following statistics:

- The numbers and percentage of subjects experiencing any TEAE;
- The numbers and percentage of subjects experiencing grade 3 or 4 TEAEs;
- The numbers and percentage of subjects experiencing TEAES that investigator found having a reasonable possibility related to veliparib/placebo;
- The numbers and percentage of subjects experiencing grade 3 or 4 TEAES that investigator found having a reasonable possibility related to veliparib/placebo;
- The numbers and percentage of subjects experiencing TEAEs that led to study discontinuation due to disease progression or not due to disease progression;
- The numbers and percentage of subjects experiencing TEAEs that led to veliparib/placebo/carboplatin/etoposide discontinuation due to disease progression or not due to disease progression;
- The numbers and percentage of subjects experiencing TEAEs that led to veliparib/placebo/carboplatin/etoposide reduction, interruption, or delay. If an AE led to more than one actions, consider them as one;
- The numbers and percentage of subjects experiencing any serious TEAE;
- The numbers and percentage of subjects experiencing any serious TEAE that investigator found having a reasonable possibility related to veliparib/placebo;
- The numbers and percentage of subjects experiencing any TEAE of special interest;
- The numbers and percentage of subjects experiencing any grade 3 or 4 TEAE of special interest;
- Listing of TEAEs that led to death;
- The numbers and percentage of subjects experiencing TEAEs that led to death;
- The numbers and percentage of subjects experiencing TEAEs that led to death that investigator found having a reasonable possibility related to veliparib/placebo;

11.3   Deaths

The number of subject deaths will be summarized 1) for deaths occurring within 30 days of the last dose of study drug in combination period, 2) for deaths that occurred more than

30 days of last dose of study drug in combination period, 3) for all deceased subjects. Death causes under each category will also be summarized.

11.4   Analysis of Laboratory

Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Post-baseline measurements collected 30 days after last dose of study drug in combination period will not be included. Last dose here will be determined by each analysis period.

<u>Analyses of Shift from Baseline in Clinical Laboratory Data</u>

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0 grades. The baseline and maximum grades are defined respectively as the baseline grade and as the highest (worst) grade during post-baseline visit on or prior to 30 days of last study drug. Section 6.0 describes the analysis convention for laboratory values used in summary of shift from baseline analyses. Baseline NCI CTCAE version 4.0 grades and maximum post-baseline grades, as well as shifts from baseline grade 0 - 2 to maximum grade 3 - 4, will be assessed by cross-tabulation for both chemistry and hematology. Shifts from baseline grade 0 - 2 to final grade 3 - 4 will be assessed by cross-tabulation for Proteinuria.

Detailed listings of all measurements collected in the extracted database for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

12.0   Timing of Efficacy Analyses and Safety Evaluations

The model-based prediction estimated Sep. 14th, 2018 as the date of 126 PFS events across the three arms. To operationalize the data acquisition and cleaning efforts in a timely manner, all efficacy and safety data through Sep. 14th, 2018 will be retrieved and entered into the clinical database prior to breaking the study blind. When the data

collection is completed and reviewed for completeness and all data management quality assurance (QA) and quality control (QC) procedures are performed, the study blind will be broken and clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data.

13.0　　　　References

1. Common Terminology Criteria for Adverse Events, Version 4.0. DCTD, NCI, NIH, DHHS. 28 May 2009 [cited 29 July 2009]. Available from: http://ctep.cancer.goveliparib/placeborotocolDevelopment/electronic_applications/ docs/ctcaev4.pdf. Updated Version 4.3. 14 June 2010. Available from: http://eversusnci.gov/ftp1/CRCAE/About.html.

2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

14.0　　　Appendix

14.1　　　DMC Charter 2017

DATA MONITORING COMMITTEE (DMC) AGREEMENT

TITLE:	**A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer**
PROTOCOL:	M14-361
AUTHORS:	
VERSION:	2.0
DATE:	24 Apr 2017

M14-361 DMC CHARTER SIGNATURES

TITLE: A Phase 1 Dose Escalation and Phase 2 Randomized
Double-Blind Study of Veliparib in Combination with
Carboplatin and Etoposide as a Therapy of Treatment-
Naïve Extensive Stage Disease Small Cell Lung Cancer

STUDY NUMBER: M14-361

I have read this DMC Agreement and confirm that to the best of my knowledge it accurately describes the conduct of the DMC.

Data Monitoring Committee Members		
███████████████████████████		Date
███████████████████████████		Date
███████████████████████████		Date

Table 1

Terms and Abbreviations

Study Team	Composed of AbbVie employees directly involved in the implementation, execution, analysis or reporting of AbbVie Study M14-361
Asset Leadership Board (ALB)	AbbVie senior management team responsible for the veliparib development strategy
DMC	Data Monitoring Committee composed of personnel noted in Section 14.1.2
IRT	Interactive response technologies
IRB/EC	Institutional Review Board/Ethics Committee
SME	Subject Matter Expert
Asset Development Team (ADT)	AbbVie team responsible for executing the development strategy developed by the ALB
DSS	Data and Statistical Sciences
Clinical Strategy Team	AbbVie multi-disciplinary team, responsible for establishing and executing the clinical development strategy for a compound (overall by indication)
Project Leader	AbbVie senior manager responsible for veliparib development and strategy
Therapeutic Area Medical/Scientific Director (TA MD/SD)	Refers to a Medical or Scientific Director from either Pharmaceutical Development or Global Medical Affairs Therapeutic Area (TA)
Clinical Scientist	AbbVie Clinical Scientist responsible for assisting the TA MD/SD with execution of AbbVie Study M14-361, including the design, conduct, analysis, and reporting of clinical trial results

14.1.1 Introduction

AbbVie Study M14-361 is a Phase 1, open-label, dose escalation/Phase 2 randomized double-blind clinical trial of veliparib in combination with carboplatin and etoposide and maintenance veliparib monotherapy. Subjects enrolled in the Phase 2 portion will be randomized in a 1:1:1 ratio to the following three treatment arms:

- Arm A: veliparib + carboplatin and etoposide followed by veliparib monotherapy;
- Arm B: veliparib + carboplatin and etoposide followed by placebo monotherapy; and
- Arm C: placebo + carboplatin and etoposide followed by placebo monotherapy.

A safety Data Monitoring Committee (DMC) will be set up for the Phase 2 portion of the study to review the aggregate unblinded safety data.

Phase 2 portion of the study:

Primary Objective of the DMC:

To evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.

This DMC Agreement defines the roles and responsibilities of the DMC, including its membership, scope, timing of meetings, and communication plan.

14.1.2 Membership

14.1.2.1 Members

The DMC consists of a Senior Medical Director who will serve as the Chair, as well as an Associate Medical Director and a Statistician who will serve as DMC members. No

DMC members will be from the Study Team responsible for conduct of the AbbVie Study M14-361.

The DMC members will review unblinded aggregate safety data by treatment group. In general, these data will not be shared outside the DMC. However, if deemed necessary by the DMC, ALB members (excluding any who are also Study Team members) may be asked to review the unblinded results with the DMC and these unblinded data can be shared with ALB members (excluding any who are also Study Team members) to support critical program needs. ALB members who are also Clinical Strategy Team members will not share any reviewed results with non-ALB Clinical Strategy Team members until study completion.

DMC Members

Member Name	Title

14.1.2.2   Duration of Membership

DMC membership will extend from the initiation of the Phase 2 portion of the study through completion of the trial. If a DMC member leaves the committee, a replacement will be selected by the TA MD/SD.

14.1.3   Role of the DMC

The DMC will provide an independent internal review and assessment of the unblinded aggregate safety data from AbbVie Study M14-361. The primary role of the DMC is to make a recommendation to the AbbVie Contact based on the unblinded analysis of available interim safety data.

The DMC will not evaluate efficacy data such as Progression Free Survival (PFS) and Overall Survival (OS). However, the incidence (rate) of subject death is considered a safety endpoint. A significant imbalance in death rate favoring the control arm (ARM C) may require action.

During the conduct of the study, the medical and safety team will monitor blinded subject laboratory results and serious adverse event data on a real-time basis. The TA MD/SD will also review blinded aggregate safety data on a regular basis and may enlist the assistance of the DMC at any time to evaluate any identified safety trend. The timeframe for trend analysis will be defined by the TA MD/SD in consultation with the DMC Chair on a case-by-case basis, depending on the nature of the safety signal.

14.1.3.1   Safety Monitoring Guidelines

The following safety data recorded in the clinical trial database will be reviewed overall and between treatment arms:

- Subject disposition;
- Dose intensity and dose reduction/interruption summary for study drug (veliparib);
- Treatment-emergent adverse events (AEs);
- AEs/SAEs relationship to study drug (veliparib);
- Treatment-emergent serious adverse events (SAEs);
- AEs leading to dose reduction/interruption of study drug (veliparib);
- Discontinuation of study drug (veliparib) due to AEs not related to disease progression;
- AEs leading to dose reduction/interruption of chemotherapy;
- Rates of death; and
- Laboratory data.

14.1.4   ORGANIZATIONAL FLOW

The DMC statistician member will be responsible for providing the unblinded analysis of the safety data required by the DMC. When the data collection and cleaning is completed for interim analysis, the clinical database will be extracted (versioned) for statistical analysis at least 10 business days prior to a scheduled DMC meeting. The DMC statistician will receive access to the necessary randomization information and statistical programs needed to generate unblinded information (tables, figures and listings) at least 7 business days prior to a scheduled DMC meeting. In turn, the DMC statistician will communicate the unblinded information to other DMC members through use of a private, limited-access SharePoint folder approximately 5 business days prior to the scheduled DMC meeting.

14.1.5   MEETINGS

14.1.5.1   Organizational Meeting

The first meeting of the DMC will be an organizational meeting. Attendees will include, but may not be limited to, the DMC members and the appropriate representatives from the Clinical Strategy Team, including the TA MD/SD, as well as Study Team members. This meeting will formally establish the DMC, thoroughly acquaint the DMC with the protocol and the DMC Agreement, and review the analysis plan for interim safety monitoring.

14.1.5.2   DMC Review Meetings

The initial DMC review meeting is planned to occur once the first 30 Phase 2 subjects complete combination treatment. Based on this initial safety DMC review, the frequency of subsequent safety DMC review meetings will be determined.

The initial safety DMC review may occur sooner than planned if the observed rate of dose-limiting toxicity (DLT)-like events in the aggregate blinded safety review of the first 15 Phase 2 subjects exceeds the rate observed in the Maximum Tolerated Dose/Recommended Phase 2 Dose (MTD/RPTD) cohort from the Phase 1 portion of the study by more than 10%. If that occurs, the DMC will convene as soon as possible to

review the aggregate unblinded safety data. A minimum of one Medical Director DMC member and the DMC statistician will have to be present to review the unblinded safety data if an immediate DMC meeting is called and other members cannot attend in the required timeframe.

The DMC Chair may request additional meetings as needed for safety reasons only.

14.1.5.2.1   Open Session

The open session attendees will include, but may not be limited to, the DMC members and the appropriate representatives from the Clinical Strategy Team, including the TA MD/SD, as well as Study Team members. The study statistician will produce and distribute Open reports to the Open Session attendees. Open reports will include tables to summarize subject accountability (number of subjects randomized, treated, discontinued and ongoing, demographic characteristics, reasons for study discontinuation and adverse event summaries). These Open reports will be aggregated across treatment arms. No unblinded information will be provided in the Open reports.

During the Open Session, the TA MD/SD and/or Clinical Scientist will provide a general update on the study and any relevant new information regarding the product under investigation, including any relevant recent literature. The TA MD/SD and/or Clinical Scientist will review the Open report with the DMC. The Study M14-361 study team can attend Open Sessions.

14.1.5.2.2   Closed Session

The DMC statistician member will provide the unblinded analysis results of the safety data as indicated in the safety monitoring guidelines (Section 14.1.3.1) to the meeting attendee's approximately 5 business days prior to the scheduled review meeting. Closed Sessions in which unblinded safety data are reviewed will be restricted to DMC members, however, the DMC may invite additional AbbVie subject matter experts (SMEs) to attend the closed sessions if the DMC determines they need to consult with AbbVie personnel

having expertise not represented on the DMC. If an SME is asked to join the closed
session, the SME must not be participating in the Veliparib program.

14.1.6   Communication

The DMC members are to treat all communications regarding this clinical study,
including reports, data, review meeting discussions, teleconferences, and meeting
minutes, as confidential material.

A private, limited-access SharePoint folder will be created to facilitate communication
between DMC members. The DMC will not share the study results with external parties
or to the non-ALB Clinical Strategy Team members/Study Team until study completion;
only the DMC recommendation may be disseminated, as applicable.

14.1.6.1   Meeting minutes

The DMC Chair or a designated member of the DMC will prepare meeting minutes for
both the open and closed sessions. Draft open session minutes will be distributed to the
meeting attendees for review within one week of the meeting. Draft closed section
minutes will be distributed to DMC members only, within one week of the meeting.
Formal open and closed session minutes will be available within one month following the
meeting(s). The DMC Chair or designee is responsible for archiving the
recommendations, the meeting materials, and minutes in the private, limited-access
SharePoint folder.

The Study Project Manager will be responsible for documenting the outcome of each
meeting in the trial master file at the end of the study (after the study has been unblinded).

14.1.6.2   Recommendations

After completing its review, the DMC may recommend to:

- Continue the trial without modification;
- Continue the trial with modification(s);

- Suspend opinion pending additional analyses;*
- Terminate the trial due to safety-related concerns;
- Other action with justification**

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* *The study statistician will generate any additional requested blinded analyses. The DMC statistician will generate any additional requested unblinded analyses.*

** *For example, communication of findings to Investigators and/or IRB/EC if there is urgency beyond what is achievable with a protocol amendment.*

The Project Leader for veliparib will serve as the AbbVie Contact for this study. The DMC will provide a completed recommendation form (see Appendix 14.1.7) to the AbbVie Contact via email immediately after the completion of the closed session.

The AbbVie Contact will have the responsibility for reviewing and communicating with the veliparib ALB in order to decide whether to accept, modify or reject the DMC recommendation. If the DMC recommendation is to continue the trial without modification, then the AbbVie Contact should communicate this information to the Study M14-361 study team directly.

If the DMC recommendation is to (a) terminate the trial due to safety-related concerns or (b) continue the study with modification(s) (e.g.,: implement "major" unplanned changes to the study protocol), the AbbVie Contact will communicate the DMC recommendation to the veliparib ALB within 24 hours, who will make a final decision regarding the necessary action to be taken based on the DMC recommendation. The ALB meeting must include Jiang Qian as an ad-hoc member to represent Data and Statistical Sciences (DSS). If the ALB determination is to either (a) accept with modification or (b) reject the DMC's recommendation, the ALB should meet with the DMC to review this decision. The ALB may need to review the same unblinded information that was made available to the DMC when they formulated their recommendation. The ALB decision will be communicated to the Study M14-361 study team, who will be responsible for executing the directive from the ALB. Affected members of the veliparib ADT and CST will be notified of this decision in a timely manner.

14.1.7   APPENDIX

Documentation of Recommendation

TITLE: A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer

STUDY NUMBER: M14-361

After reviewing the unblinded interim safety data (Version X, XXX 201X), the DMC recommends to:

☐   Continue the trial without modification

☐   Continue the trial with modification(s) (as described below)

☐   Suspend opinion pending additional analyses

☐   Terminate the trial due to safety-related concerns

☐   Other action with justification (as described below)

_____

_____

_____

_____

I acknowledge that this is the joint recommendation of the Data Monitoring Committee.

Date

Date

Date

14.1.8 APPENDIX

<u>Changes from Previous Version</u>

● Title page: Updated version number from 1,0 to 2.0; updated version date from 27 Mar 2017 to 24 Apr 2017; Updated footer to reflect new date 24 Apr 2017

● Table of Contents: Added new Appendix II, Changes from Previous Version

● Page 1: Updated footer to reflect new version/date; Updated Data Monitoring Committee Member from ███

● Pages 4 and 9: Updated Data Monitoring Committee Member from ███

14.2 List of Abbreviations

● AE: Adverse Event
● ANCOVA: Analysis of Covariance
● AST: As-Treated
● ATDI: Actual total dose intensity
● BID: Twice A Day
● CMH: Cochran-Mantel-Haenszel
● CR: Complete Response
● CTCAE: Common Terminology Criteria for Adverse Events
● DI: Dose intensity
● DLT: Dose Limiting Toxicity
● DMC: Data Monitoring Committee
● DOR: Duration of Overall Response
● ECOG: Eastern Cooperative Oncology Group
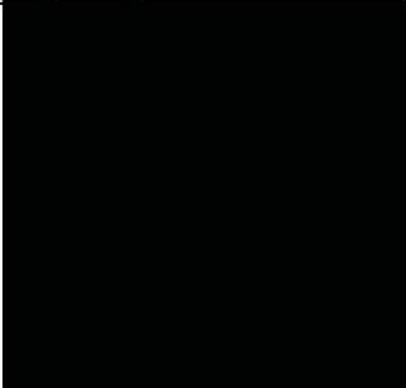● eCRF: Electronic Case Report Form

- ED SCLC: Extensive Stage Disease Small Cell Lung Cancer
- FDA: Food and Drug Administration
- IRT: Interactive Response Technology
- ITT: Intent-To-Treat
- IV: Intravenous
- LDH: Lactate Dehydrogenase
- MTD: Maximum Tolerated Dose
- NCI: National Cancer Institute
- ORR: Objective Response Rate
- OS: Overall Survival
- PD: Disease Progression
- PFS: Progression Free Survival
- PR: Partial Response
- PTDI: Planned total dose intensity
- QA: Quality Assurance
- QC: Quality Control
- RPTD: Recommended Phase Two Dose
- Rx: Medical Prescription
- SAE: Serious adverse event
- SmPC: Summary of Product Characterizations
- ULN: Upper Limit of Normal

Document Approval

Study M14361 - Statistical Analysis Plan Version 1 - 15Nov2018 (E3 16.1.9)

Version: 1.0   **Date:** 15-Nov-2018 10:55:23 PM   **Company ID:** 11152018-00F9F683F68CF7-00001-en

Signed by:	Date:	Meaning Of Signature:
███████████	15-Nov-2018 07:11:29 PM	Approver
	15-Nov-2018 07:15:59 PM	Approver
	15-Nov-2018 08:12:44 PM	Approver
	15-Nov-2018 08:47:13 P	Approver
	15-Nov-2018 08:49:45 PM	Approver
	15-Nov-2018 10:55:22 PM	Approver