Statistical Analysis Plan

I3Y-MC-JPBO: A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma

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1. Statistical Analysis Plan
I3Y-MC-JPBO: A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma

Abemaciclib (LY2835219)

This study is a global, multicenter, open-label, Phase 2 trial of abemaciclib in patients with brain metastases secondary to hormone receptor positive breast cancer.

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Statistical Analysis Plan V1 electronically signed and approved by Lilly: 12 Feb 2015
Statistical Analysis Plan V2 electronically signed and approved by Lilly
on date provided below.

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first patient visit.

SAP Version 2 was approved on 09-August-2018. The rationale for SAP version 2 was to incorporate changes to the protocol in amendments JPBO(b) and JPBO(c). Based on amendment JPBO(b), Part D, Part E and Part F were added and incorporated into the study objectives. Based on amendment JPBO (c), Simon two-stage analyses are based on evaluable patients. More details were added to Section 6.1.1 Populations. More details for derivations of BOIR and BOR were added to Section 6.7.2 Secondary outcome and Methodology.

4. Study Objectives

4.1. Primary Objective

The primary objective of study I3Y-MC-JPBO (JPBO) is to evaluate abemaciclib with respect to objective intracranial response rate (OIRR; complete response [CR] + partial response [PR]) based on tumor assessments and brain metastases response criteria (see protocol attachment 5):

- in women with brain metastases secondary to HR+, HER2+ breast cancer.
- in women with brain metastases secondary to HR+, HER2- breast cancer.
- in patients with brain metastases secondary to NSCLC.
- in patients with brain metastases secondary to melanoma.

4.2. Secondary Objectives

The secondary objectives of the study are as follows:

To evaluate abemaciclib with respect to:

- Intracranial disease per brain metastases response criteria
    - Best overall intracranial response (BOIR)
    - Duration of intracranial response (DOIR) (CR + PR)
    - Intracranial disease control rate (IDCR) (CR + PR + stable disease [SD])
    - Intracranial clinical benefit rate (ICBR) (CR + PR + SD≥6 months)
- Overall
    - OS
    - Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and RANO-BM
    - Disease control rate (DCR) (CR+ PR+ SD) per RECIST v1.1 and RANO-BM
    - Progression-free survival (PFS) per RECIST v1.1 and RANO-BM
- Change in symptoms as assessed by MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)
- Safety and tolerability
- PK of abemaciclib and its metabolites

4.3. Exploratory Objectives

- To explore change in neurocognitive function as assessed by Trail Making Tests A and B

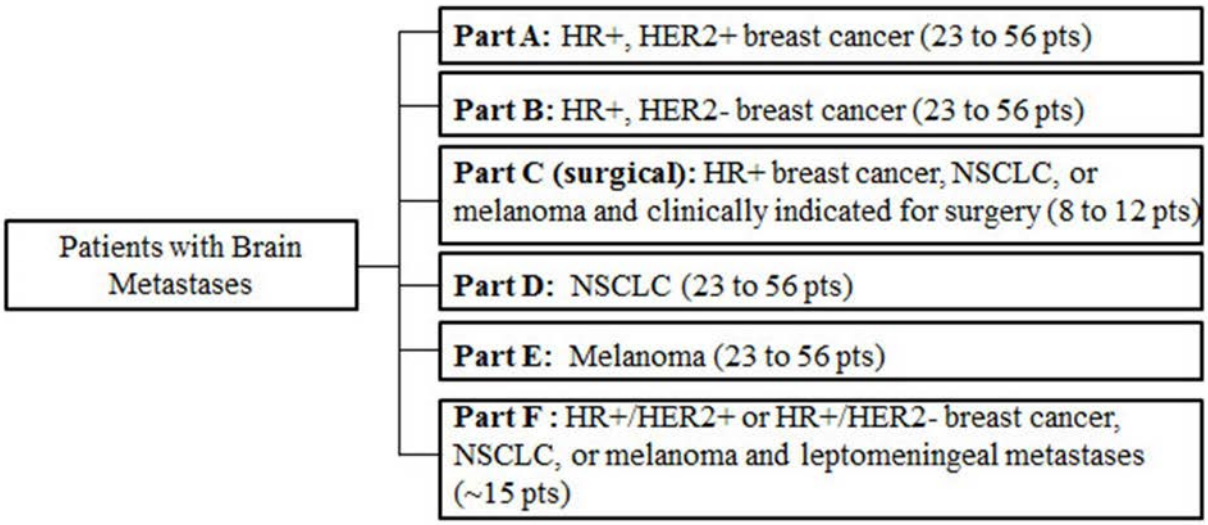
- To explore change in neurologic signs as assessed by the Neurologic Assessment in Neuro-Oncology (NANO) scale
- To explore the concentration of abemaciclib and its metabolites in plasma, cerebrospinal fluid (CSF), and brain tumor tissue collected at the time of surgical resection for patients participating in Part C, as well as concentrations in time-matched samples of plasma and CSF for patients participating in Part F.
- To explore biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of HR+ breast cancer, NSCLC, and melanoma
- To assess the effect of abemaciclib on leptomeningeal metastases (LM) in patients with HR+ breast cancer, NSCLC, or melanoma based on proposed RANO-LM response criteria
- To explore the relationship between abemaciclib exposure and response

5. Study Design

5.1. Summary of Study Design

Study JPBO is a multicenter, open-label, Phase 2 trial of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC or melanoma.

Figure 5.1 illustrates the study design.



* All patients in Parts A, B, D, E, and F will receive abemaciclib PO Q12H until PD, unacceptable toxicity, or withdrawal from the study. Patients in Part C will receive abemaciclib PO Q12H for 5 to 14 days prior to surgical resection; dosing may resume after a wound healing period and continue until PD, unacceptable toxicity or withdrawal.

Abbreviations: HER2+ = HER2 positive; HER2-= HER2 negative; HR+ = hormone receptor positive; mg = milligrams; NSCLC = Non-small cell lung cancer; PD = progressive disease; PO = orally; pts = patients; Q12H = every 12 hours.

Figure 5.1. Illustration of study design.

5.2. Determination of Sample Size

Separate Simon 2-stage designs (Simon 1989) will be employed for Part A, Part B, Part D and Part E. Each design assumes a 1-sided type-I error of 0.05 and 80% power.

For Part A, 23 qualified patients will be enrolled in the first stage. If at least 2 of the first 23 evaluable patients respond to therapy, accrual will continue until 33 additional evaluable patients have been enrolled in second stage. A total of 6 responders out of 56 evaluable patients in Part A would need to be observed to warrant further investigation of abemaciclib in this patient population.

The procedure described above tests the null hypothesis (H_0) that the true OIRR of abemaciclib in Part A is ≤5% versus the alternative hypothesis (H_a) that the true OIRR is ≥15%. The probability of early termination of the treatment arm under H_0 is 0.68.

Part B, Part D and Part E will have the identical design as Part A.

Assuming approximately 20% screening failure, the study will enter approximately 309 patients.

6. A Priori Statistical Methods

6.1. General Consideration

Statistical analysis of this study will be the responsibility of Lilly.

All tests will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Unless otherwise stated, all analyses will be conducted on each study part separately. Pooled analyses including patients from all parts will be conducted when applicable.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

6.1.1. Populations

The **entered** population includes all patients who sign the informed consent document.

The **Full Analysis Set (FAS)** includes all enrolled patients receiving at least 1 dose of abemaciclib.

The **OIRR evaluable population** includes all enrolled patients receiving at least 1 dose of abemaciclib who have at least one measurable brain lesion at time of enrollment (per RANO-BM) and for whom at least one post-baseline overall response assessment for intracranial disease is available.

Safety analyses will be conducted on the **Full Analysis Set (FAS)**. Efficacy analyses will be conducted in the FAS population and in the OIRR evaluable population when appropriate, including the following.

Endpoint	Analysis Population
Objective Intracranial Response Rate	FAS OIRR evaluable population
Best overall intracranial response (BOIR)	FAS OIRR evaluable population
Duration of intracranial response (DOIR) (CR + PR)	FAS OIRR evaluable population
Intracranial disease control rate (IDCR)	FAS OIRR evaluable population
Intracranial clinical benefit rate (ICBR)	FAS OIRR evaluable population
Objective response rate (ORR) per RECIST v1.1 and RANO-BM	FAS FAS Patients with extracranial disease
Best overall extracranial response (BOR)	FAS FAS Patients with extracranial disease
Disease control rate (DCR)	FAS FAS Patients with extracranial disease
Overall survival (OS)	FAS OIRR evaluable population
Bicompartamental Progression-free survival (PFS)	FAS OIRR evaluable population
Intracranial Progression-free survival (PFS)	FAS OIRR evaluable population
Extracranial Progression-free survival (PFS)	FAS FAS Patients with extracranial disease
Intracranial tumor data	OIRR evaluable population
Extracranial tumor data	FAS Patients with extracranial disease

PK analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected.

Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

6.1.2. Definitions and Conventions

Study drug refers to LY2835219 (abemaciclib).

The **date of first dose** is the date of the first dose of study drug.

The **baseline** value of an assessment is the last value observed prior to the first dose of study drug.

The **study day** of an event or assessment will be calculated as the difference between the day of the event or assessment and the date of first dose plus 1. For example, if an event occurs on 08JUN2014 and the date of first dose was 06JUN2014, the study day of the event is 3.

One **month** is defined as 365/12 days.

6.2. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed. The method of imputation for any dates that are imputed is described in the relevant section.

6.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, treated in the study, reasons for discontinuation from study treatment and reasons for discontinuation from study. Reason for discontinuation from both study treatment and the study will be summarized by pre-determined categories. If the reason for discontinuation is adverse event (AE), the associated AE term will be reported.

A summary of all important protocol deviations will be provided.

6.4. Patient Characteristics

6.4.1. Baseline Demographics and Patient Characteristics

Patient demographics and baseline disease characteristics will be listed for all patients on therapy and summarized by study part.

Patient demographics will include sex, race, age, height, weight, and body mass index (BMI). Baseline disease characteristics will include basis for diagnosis, initial pathological diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, number of target brain lesions and location of extracranial lesions

6.4.2. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Term(s) [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be summarized.

6.4.3. Prior Therapies

Prior radiotherapy, surgery, and systemic therapy will be summarized. Prior radiotherapy and surgery will be categorized by reason for regimen. Prior systemic therapies will be categorized by reason for regimen ([neo]adjuvant therapy or therapy for locally advanced or metastatic disease) and specific therapy. Frequency of each specific therapy will be tabulated within each reason for therapy.

Prior local therapy for target brain lesions will be summarized by therapy category (whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) or surgical resection or not done)

Most recent systemic therapy and the duration of that therapy will be summarized within each of the following subgroups:

- Patients whose most recent systemic therapy was an adjuvant therapy
- Patients whose most recent systemic therapy was for locally advanced or metastatic disease.

This summary will include median duration of treatment (date of end of therapy – date of start of therapy + 1), median time to progression (date of progression – date of first dose + 1), and frequency of each specific therapy. If only the month and year of a treatment date or progression date is available, the day will be imputed to the 15th.

6.4.4. Post Study Treatment Discontinuation Therapies

Systemic therapies and intracranial therapies received following study treatment discontinuation will be summarized overall and by category.

6.5. Treatment Compliance

Treatment compliance of abemaciclib will be measured by pill counts and summarized by cycle. Within each cycle, compliance will be calculated as the ratio of total dose taken to the total assigned dose (minus any dose adjustments and doses omitted/withheld for medical reasons). The total assigned dose for a patient with no adjustments or omissions is 200 mg per dose × 2 doses per day × 21 days = 8400 mg.

6.6. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized for the FAS population using the preferred name. Corticosteroids usage and dose changes will be summarized by study part.

6.7. Efficacy Analyses

6.7.1. Primary Outcome and Methodology

The primary efficacy measure is OIRR (CR + PR) as defined by RANO-BM. A partial intracranial response is defined as ≥30% decrease in sum of LD of up to 5 target brain lesions sustained for at least 4 weeks in the absence of progression of nonmeasurable brain lesions, new brain lesions, increased corticosteroid dose, or clinical worsening. Radiologic PD is defined as ≥20% increase in sum of LD of up to 5 target brain lesions from the nadir with at least one target nrain lesion incresing by 5 mm or more, unequivocal progression of at least on non-target brain lesion, or the appearance of an unequivocal new brain lesion. Clinical PD is neurologic deterionation or worsening of disease status.

Best response is determined from the sequence of responses assessed. If the first assessments are radiologic SD and clinical PD on the same day then best response will be determined to be PD.

A second assessment must be performed ≥28 days after the first evidence of response (CR or PR). Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying as a

CR, are required for a best response of PR. Best response of SD is defined as disease that does not meet the criteria for CR, PR, or PD and has been evaluated at least 1 time, at least 35 days after the start of abemaciclib. If there is only one SD on or after day 35 and no other assessment then BOIR is SD. If there is only one SD prior to day 35 and no other assessment then BOIR is NE.

Best response will be derived to encompass all tumor assessments from baseline until the earliest of objective progression or start of new anticancer therapy. Any responses observed after objective progression or the start of new anticancer therapy are excluded from the determination of best response.

The date of first documented objective disease progression must be recorded on the eCRF even if it occurs after the patient has started a new therapy.

Lilly or its designee will collect and store tumor assessment images (including photographs of visible lesions), and an independent review of imaging scans may be performed by Lilly or its designee.

The OIRR is estimated as the total number of confirmed CRs and PRs divided by the total number of evaluable patients enrolled. The primary analysis of OIRR for each study Part (A, B, D, or E) will occur approximately 6 months after up to 56 patients have been enrolled into each respective part. This is to ensure adequate durability of response data is available at the time of analysis.

6.7.2. Secondary Outcome and Methodology

The secondary objectives for this study are stated in section 4.2; secondary efficacy measures are defined in protocol section 10.1.4.

Point estimates and 95% CIs (using the normal approximation to the binomial) will be calculated for BOIR, IDCR, ICBR, ORR, and DCR for Part A , Part B, Part D and Part E.

Best overall intracranial response

Best overall intracranial response (BOIR) is derived to encompass all tumor assessments (according to RANO-BM) from baseline until the earliest of objective progression (intracranial or extracranial according to RANO-BM or RECIST v1.1, respectively) or start of new anticancer therapy. Any responses of RANO-BM observed after objective intracranial progression or the start of new anticancer therapy are excluded from the determination of BOIR. Any responses of RANO-BM observed after objective extracranial progression which occur at a later cycle than the extracranial progression will be excluded from the determination of BOIR. However, any responses of RANO-BM observed after objective extracranial progression which occur at the same cycle as the extracranial progression will be included in the definition of BOIR, even it occurs after the extracranial progression. Each patient's BOIR will be categorized as CR, PR, SD, PD, or NE.

Best overall extracranial response

Best overall extracranial response (BOR) is derived to encompass all tumor assessments (according to RECIST 1.1) from baseline until the earliest of objective progression (intracranial or extracranial according to RANO-BM or RECIST 1.1, respectively) or start of new anticancer therapy. Any responses of RECIST 1.1 observed after objective extracranial progression or the start of new anticancer therapy are excluded from the determination of BOR. Any responses of RECIST 1.1 observed after objective intracranial progression which occur at a later cycle than the intracranial progression will be excluded from the determination of BOR. However, any responses of RECIST 1.1 observed after objective intracranial progression which occur at the same cycle as the intracranial progression will be included in the definition of BOR, even it occurs after the intracranial progression. Each patient's BOR will be categorized as CR, PR, SD, PD, or NE.

Time-to-event efficacy endpoints (OS, PFS, and DOIR) will be summarized for Part A, B, D and E using Kaplan-Meier techniques (Kaplan and Meier 1958) if there is sufficient data. If performed, Kaplan-Meier curves will be generated, and quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% CIs (Brookmeyer and Crowley 1982).

6.7.3. Exploratory Outcome

Investigator-assessed leptomeningeal metastases responses will be summarized for Part F. Neurological assessment in Neuro-Pncology (NANO) scale, CSF cytology, neuroimaing assessment, and symptoms will be listed.

6.8. Health Outcomes/Quality-of-Life Analyses

Patient-reported outcomes are measured through paper versions of MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT)

Patients with at least 1 baseline and at least 1 postbaseline assessment will be included in the analyses. Compliance with completing the questionnaires will be summarized at the group-level at each assessment period (defined as the number of completed questionnaires/number expected questionnaires given those that are still on study). Reason for missing questionnaires will be assessed.

Data will be summarized for each study part (Parts A, Part B , Part D and Part E) and response category (CR/PR, SD, PD); change from baseline and time to worsening will be explored. This summary will include mean, standard deviation, median, minimum, maximum, and change from baseline. The MDASI-BT will be reported as core symptoms, brain tumor symptoms, symptom interference, and symptom groupings (affect, cognition, focal neurologic deficit, treatment-related symptoms, generalized/disease status symptoms, and gastrointestinal symptoms). Time to worsening will be described for these categories.

Additional exploratory analysis will be described in a separate health outcome analysis plan.

6.9. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK) analyses will be performed according to a separate PK analysis plan.

6.10. Tailoring Biomarker Analyses

Analysis of biomarkers will be described in a separate biomarker SAP.

6.11. Safety Analyses

6.11.1. Extent of Exposure

For abemaciclib, extent of exposure will be measured by pill counts and summarized by cycle and cumulatively. The summary will include total dosage taken and dose intensity. Dose intensity will be calculated as the ratio of total dose taken to the assigned cumulative dose. The assigned cumulative dose for each patient during each cycle is 200 mg per dose × 2 doses per day × 21 days = 8400 mg. The assigned cumulative dose while on study is 8400 mg × number of cycles started.

Dose adjustments and omissions, along with the reason for adjustment or omission, will be summarized.

6.11.2. Adverse Events

Verbatim text for the adverse events will be entered by the investigator , as well as the adverse event (AE) terms and severity grades per CTCAE Version 4.0.

Since all the terms in CTCAE Version 4.0 are themselves LLTs of MedDRA, adverse events will be handled in the following manner:

- The CTCAE Version 4 term reported by the investigator will be mapped to the corresponding MedDRA PT and system organ class (SOC), unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify' the MedDRA LLT, PT and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Serious adverse event (SAE) and relationship of AE to the study drug are defined in protocol section 10.3.1.1. The derivation of treatment emergent adverse event (TEAE) is described in protocol section 12.2.11.

Overview of adverse event will be summarized for abemaciclib. The following TEAE/SAE listings and summaries will be produced:

- Summary of TEAEs by PT (all grade and grade ≥3)
- Summary of TEAEs by SOC and PT (all grade and grade ≥3)
- Summary of TEAEs by PT and maximum grade (1-5)
- List of SAEs

- Summary of SAEs by SOC and PT (all grade and grade ≥3)

The four summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related to study treatment.

6.11.3. Deaths

All deaths on study not attributed to study disease by the investigator will be listed along with the reason for death, if known. For those deaths attributed to an AE, the listing will include the PT of the AE. A summary of deaths including reasons for death will be produced.

6.11.4. Clinical Laboratory Evaluation

All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 4. These calculated grades will be summarized by cycle and maximum post-baseline grade over the entire study.

6.11.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, weight and ECOG PS will be summarized by cycle.

6.11.6. Electrocardiograms

Local electrocardiograms (ECGs) will be summarized by cycle and overall. The summary by cycle will classify patients as having normal or abnormal ECG and summarize AEs identified by ECG within each cycle. The overall summary will classify patients as having an abnormal ECG at any point and summarize all AEs identified by ECG.

6.11.7. Hospitalizations and Transfusions

The frequency and percentage of patients with any hospitalizations experienced during the study treatment period or 30-day post discontinuation follow-up period will be summarized by treatment arm and best response category.

6.12. Subgroup Analysis

Subgroup analyses of OIRR will be performed for each subgroup variables:

- Age (<65 years vs. ≥65 years)
- Region (North America vs. Europe vs. Asia vs. Other)
- Race (Caucasian vs. Asian vs. Other)
- Prior brain metastases therapy (yes vs. no)Concurrent endocrine therapy (yes vs. no)

Graded Prognostic Assessment (GPA) score (<3 vs. ≥3)If a level of a factor consists of fewer than 10% of enrolled patients, analysis within that level will be omitted.

Other exploratory subgroup analyses may be performed as deemed appropriate.

6.13. Interim Analysis

The Simon 2-stage design has a built-in interim analysis to analyze OIRR and to meet threshold continuation criteria. The interim analysis of OIRR for each study part (Part A, Part B, Part D and Part E) will occur 6 months after the 23rd evaluable patient is enrolled into each respective part. This is to ensure adequate durability of response data is available at the time of analysis. This interim analysis for response must be strictly followed to preserve the statistical properties of the Simon 2-stage design. Due to this requirement, objective data will be obtained to document response and to determine if the trial is to continue based on the OIRR. Because of this, no Assessment Committee or Data Monitoring Committee will be convened to oversee this trial.

Additional interim analyses will be planned if deemed necessary.

6.14. Protocol violation

Protocol violations that can be derived from the data and are related to inclusion/exclusion criteria or treatment will be summarized. These violations will include those defined by:

- Inclusion/Exclusion Criteria
    - Diagnosis
    - Prior treatments received
    - Age
    - Performance Status
- Treatment
    - Dose delays
    - Dose reductions

6.15. Annual Report Analysis

Annual report analyses, including Developmental Safety Update Report (DSUR) and Investigational Brochure (IB) analyses, are described in the LY2835219 Program Safety Analysis Plan.

6.16. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. Analyses provided for the CTR requirements include the following: Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).

- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event (AE) reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

In addition, a participant flow will be created that will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study if the patient dies while on the study or the patient had discontinued study treatment and is in follow up at the time of the final OS analysis. Patients who withdraw consent before the final OS analysis or who are still on treatment at the time of the final OS analysis will be identified as not completing the study.

7. Unblinding Plan

JPBO is an open-label study.

8. References

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