A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-group Study to Assess the Safety and Efficacy of ASP4345 as Add-on Treatment for Cognitive Impairment in Subjects with Schizophrenia on Stable Doses of Antipsychotic Medication

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STATISTICAL ANALYSIS PLAN

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Astellas Pharma Global Development, Inc. (APGD)

Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
APGD	Astellas Pharma Global Development, Inc.
ASSR	auditory steady-state response
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CGI-S	Clinical Global Impression of Severity Scale
CI	confidence interval
CIAS	cognitive impairment associated with schizophrenia
C_{max}	maximum concentration
COMT	catechol-o-methyltransferase
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EoT	end-of-treatment
ET	early termination
FAS	full analysis set
HDL	high-density lipoprotein
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LDL	Low-density lipoprotein
LS	least squares
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MATRICS-CT	Measurement and Treatment Research to Improve Cognition in Schizophrenia Coprimary and Translations
MCCB	Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery
MedDRA	medical dictionary for regulatory activities
MMRM	Mixed Models Repeated Measures
NSA-16	Negative Symptom Assessment Scale
NSAIDs	non-steroidal anti-inflammatory drugs
PANSS	Positive and Negative Symptom Scale

Abbreviations	Description of abbreviations
PGx	pharmacogenetic
PKAS	pharmacokinetic analysis set
QD	daily
QTcF	QT interval using Fridericia's formula
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SE	standard error
TEAE	treatment emergent adverse events
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPSA-2-ER	University of California San Diego Performance-based Skills Assessment-2 Extended Range

List of Key Terms

Terms	Definition of terms
Baseline	The last measurement/evaluation on or prior to the first dose of randomized therapy is considered the baseline measure/evaluation.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	To register or enter a subject into a clinical trial. NOTE: Once a subject has received the study drug or placebo, the clinical trial protocol applies to the subject.
Intervention	The drug, device, 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.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to database hardlock and unblinding the subject treatment assignment.

Critical changes that affected the statistical analyses from the analyses planned in the SAP will be documented in the Clinical Study Report (CSR).

2 STUDY OBJECTIVE(S) AND DESIGN

2.1 Study Objective(s)

The objectives of the study, conducted in subjects with cognitive impairment associated with schizophrenia, are the following:

2.1.1 Primary Objectives

- To evaluate the efficacy of ASP4345 on cognitive impairment compared to placebo using change from baseline in MATRICS Consensus Cognitive Battery (MCCB) neurocognitive composite score (excluding social cognition domain). The primary estimand will use a Hypothetical Strategy and compare patients as though they had continued on the assigned treatment.
- To evaluate the safety and tolerability of ASP4345 compared to placebo

2.1.2 Secondary Objectives

- To evaluate the effects of ASP4345 compared to placebo on functional capacity using the University of California San Diego Performance-based Skills Assessment-2 Extended Range (UPSA-2-ER) total score.
- To evaluate the pharmacokinetic profile of ASP4345 and its metabolites, if necessary

2.1.3 Exploratory Objectives

- To evaluate the effects of ASP4345 compared to placebo using:
    - the 16-item version of the Negative Symptom Assessment Scale (NSA-16)
    - the individual domains of the MCCB
    - the assessment of general clinical symptoms with the Positive and Negative Symptom Scale (PANSS)
    - the assessment of the Clinical Global Impression of Severity Scale (CGI-S)
- To evaluate the relationship between the CGI-S and MCCB neurocognitive composite score
- To evaluate the relationship between number of cognitive training levels, including repeat levels, completed (as a measure of compliance with cognitive training) and MCCB neurocognitive composite score
- To evaluate the pharmacogenetic impact on ASP4345 pharmacodynamic results

2.2 Study Design

This is a randomized, double-blind, placebo-controlled, 3-arm oral dose study to evaluate the safety and efficacy of ASP4345 in subjects with cognitive impairment associated with schizophrenia on stable doses of risperidone, quetiapine, olanzapine, ziprasidone, aripiprazole, brexpiprazole, paliperidone or lurasidone for at least 4 weeks prior to screening for oral medications and 2 months for depot medications. The study will consist of the following periods:

- Screening period (up to 28 days)
- Double-blind treatment period (12 weeks/84 days)
- Follow-up period (14 days post last dose)

Approximately 420 subjects are planned to be screened with up to 210 subjects enrolled in 1 of 3 arms. Study groups will consist of approximately 90 placebo subjects and 60 subjects each per active study arm randomized in 3:2:2 ratio to receive 1 of 2 doses of ASP4345 or matching placebo daily (QD) for 12 weeks. Study treatment assignments will be according to the following table:

Group	Dose Regimen	Number
A	50 mg, QD	60
B	150 mg, QD	60
C	Placebo, QD	90

All subjects will be administered the first dose of blinded study drug at the site following randomization and provided with mobile applications that provide supplemental cognitive training and record treatment compliance. Subjects will return to the clinic weekly for safety, efficacy, and/or pharmacokinetic procedures at days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 84. Subjects will continue their antipsychotic treatment for the entire study and will be followed for 14 days after their last dose of study drug.

Subjects terminating early from the study treatment will be encouraged to complete scheduled visits. All subjects are allowed to stop study drug, but continue in the study through day 84 according to the current visit schedule unless the participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant provide this information.

2.3 Randomization

Subjects will be randomized in a 3:2:2 ratio to a treatment arm (placebo to active) according to the randomization schedules through IRT. All subjects who meet the eligibility criteria will be randomized. The site personal will dispense the treatment according to the IRT system's assignment. Randomization will occur by site (stratified by site). In order to reduce the impact of incomplete blocks at any given site, a Latin square design will be used to generate the randomization list such that blocks are balanced both in regard to the number of treatment assignments but also to the order in which treatments are assigned. Blocks will be

dynamically assigned by the IRT system to sites once they request a randomization number, so that all blocks in a Latin square will be assigned before moving on to the next Latin square.

3 SAMPLE SIZE

A total sample size of 210 subjects will be randomized in 3:2:2 ratio (approximately 90 placebo and 60 subjects each per active study arm) into 1 of 2 doses of ASP4345 or matching placebo. The sample size will provide approximately 82% power for the pairwise comparisons to placebo to detect an effect size of at least 0.43 in the primary outcome measure, assuming a 1 sided 5% significance level, with statistical significance achieved at an effect size of approximately 0.28. Note that the decision criteria to proceed with the development of the compound will be based on effect sizes rather than statistical significance. The number of subjects planned for this clinical study are considered sufficient to achieve the clinical study objectives.

4 ANALYSIS SETS

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

The determination of whether subjects are included or excluded from the safety and efficacy analysis sets will be made prior to database hard-lock. All classifications can be made programmatically and so a Classificiation meeting may not be held.

4.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are randomized and receive at least one dose of study drug and have at least one post baseline MCCB measurement. This will be the primary analysis set for efficacy analyses.

4.1.1 Modified Full Analysis Set 1

A modified full analysis set 1 (mFAS1) will be a subset of the FAS, with the exclusion of subjects whose study coordinator may have become unblinded during the study due to an error in the drug accountability system, and where the subejct's rater is the same person as the study coordinator.

4.1.2 Modified Full Analysis Set 2

A modified full analysis set 2 (mFAS2) will be a subset of the FAS, with the exclusion of subjects whose study coordinator may have become unblinded during the study due to an error in the drug accountability system.

4.2 Intent-to-Treat Set

The Intent-to-Treat analysis set (ITT) will consist of all subjects who are randomized into the study. The ITT will be used to assess the robustness of the results of the primary efficacy endpoint from the statistical tests based on the FAS. Select demographic and baseline characteristics may also be summarized for the ITT.

4.3 Safety Analysis Set

The Safety Analysis Set (SAF) consists of all subjects who took at least 1 dose of study drug, and will be used for safety analyses.

For the statistical summary of the safety data, the SAF will be used.

4.4 Pharmacokinetics Analysis Set

The pharmacokinetic analysis set (PKAS) consists of all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration.

The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

5 EFFICACY ENDPOINTS

5.1 Primary Efficacy Endpoint(s)

- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the MCCB neurocognitive composite score (excluding social cognition domain).
- Safety and Tolerability:
  - Nature, frequency and severity of AEs.
  - Vital signs (sitting or supine blood pressure, pulse and body temperature)
  - Clinical laboratory tests (hematology, biochemistry [including cystatin C, serum prolactin, and ACTH] and urinalysis)
  - Routine 12-lead ECG
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Changes in individual indices of metabolic syndrome (weight, waist circumference, cholesterol, triglycerides, high-density lipoprotein [HDL; the second screening visit and day 77), and hemoglobin A1c [HbA1c]
  - Movement disorder (Abnormal Involuntary Movement Scale [AIMS], Simpson Angus Scale [SAS] and Barnes Akathisia Rating Scale [BARS])

5.2 Secondary Efficacy Endpoints

- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the UPSA 2 ER instrument total score
- Pharmacokinetics:
  - ASP4345 and its metabolites, if necessary (plasma): C_{trough}.

5.3 Exploratory Efficacy Endpoints

- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the NSA-16 only for the subjects who have at least 1 negative symptom of at least moderate severity
- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the MCCB composite score.
- Change from baseline to week 12/EoT for ASP4345 compared to placebo for each of the MCCB domains.
- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the PANSS
- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the CGI-S

- Correlation between MCCB and CGI-S scores at each measurement (weeks -4, -3, 0, 6, 12)
- Correlation between change from baseline to week 12/EoT in MCCB and change from baseline to week 12/EoT in CGI-S scores
- Correlation between the number of cognitive training levels, including repeat levels, completed (as a measure of compliance with cognitive training) and MCCB neurocognitive composite score
- Pharmacogenetics:
    - Catechol-o-methyltransferase (COMT) and dopamine D_1 and D_3 receptor genotyping

6 STATISTICAL METHODOLOGY

6.1 General Considerations

Continuous data will be summarized descriptively including the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by frequencies and percentages. Percentages by categories will be based on the number of subjects with no missing data, i.e. the percentages for the non-missing categories will add up to 100%.

A 2-sided significance level of 0.10, unless otherwise specified, will be used for all statistical tests on efficacy endpoints without multiplicity adjustment.

All data summarization and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications.

6.2 Study Population

Analysis of the primary efficacy endpoint will be conducted on the FAS and ITT. The interpretation of results from statistical tests will be based on the FAS. The ITT will be used to assess the robustness of the results from the statistical tests based on the FAS. Analysis of the secondary and exploratory efficacy endpoints will be done on the FAS only.

Data such as patient disposition, demographics and baseline characteristics will be summarized for FAS in the event that the definition of FAS is identical to SAF (i.e., if no patients were given wrong study drug and all have a post-baseline MCCB neurocognitive composite score). If FAS is not identical to SAF then data will be summarized for both FAS and SAF as specified in the relevant sections.

6.2.1 Disposition of Subjects

Disposition of subjects will be summarized for the FAS by treatment group and overall. Number of subjects who complete or prematurely discontinue from the treatment or study (ie, follow up period) will be summarized by treatment group and overall. For the discontinuation, the primary reason reported by the investigator will be summarized.

Number and percentage of subjects for each analysis set will be summarized by treatment group and overall.

6.2.2 Protocol Deviations

The number and percentage of subjects with the following protocol deviation criteria will be summarized for each criterion and overall, by treatment group and total as well as by investigative site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion.

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.

6.2.3 Demographic and Other Baseline Characteristics

Demographic, age, sex, race, ethnicity, weight, height, BMI, and smoking status, and other baseline characteristics will be summarized descriptively by treatment group and overall for the FAS, ITT and SAF.

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

Medical and psychiatric history for each subject will be presented in a listing.

6.2.4 Previous and Concomitant Medications

Previous and concomitant medications will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the FAS. 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.

Medications taken for treatment of schizophrenia during the 12 months prior to screening and other medication taken 28 days prior to the screening visit and up to the first dose of study medication (treatment period) will be defined as prior schizophrenia medications or other prior medication, respectively. Concomitant medications are defined as any medications that patients took after the first dose of study medication and through last dose of study drug. Medications that started prior to first administration of study drug and continued while study drug was given will be counted in both previous and concomitant medications.

6.3 Study Drugs Exposure and Compliance

Duration and compliance of study drug will be summarized for FAS, ITT, and SAF by treatment group and overall.

Number and percentages of subjects with the following categories of study drug duration will be summarized: >0 to ≤ 2 days, >2 to ≤ 7 days, >7 to ≤ 14 days, >14 to ≤ 21 days, >21 to ≤ 42 days, >42 to ≤ 56 days, >56 to ≤ 84 days.

Number and percentages of subjects with the following cumulative categories of study drug duration will be summarized: ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 42 days, and ≥ 56 days.

Study drug compliance will be summarized and listed both for product accountability from an IRT system as well as from daily virtual monitoring by use of a mobile application. Product accountability will be the primary source of compliance, and % compliance will be calculated at each visit and overall as ([the number of pills dispensed] – [the number of pills returned]) / [the number of pills expected consumed] * 100, where the number of pills expected consumed is the duration in days.

6.4 Analysis of Efficacy

6.4.1 Analysis of Primary Efficacy Endpoint(s)

No multiplicity adjustment will be necessary in this study.

6.4.1.1 Primary Analysis for Primary Efficacy Endpoint(s)

Consistent with the Hypothetical Strategy used for the estimand which is to compare patients as though they had continued on the assigned treatment, MMRM will use all available on-treatment data to inform end of treatment mean treatment effect estimates without requiring explicit imputation for missing data (i.e., for discontinued subjects). There will be no adjustment made for multiple comparisons. The primary analysis will use the FAS.

The MCCB neurocognitive composite score is a standardized mean of the six domain scores (excluding social cognition). Raw scores are converted to age and sex adjusted t-scores which are standardized to normative data, and have a mean of 50 and standard deviation of 10 in the general healthy population. A higher score indicates less impairment.

The primary endpoint of change from baseline in MCCB neurocognitive composite T score will be analyzed using a Mixed Models Repeated Measures (MMRM) approach. The model will contain fixed effect terms for treatment group, pooled site, visit (the repeated term), treatment by visit, and visit by baseline, with the MCCB neurocognitive composite score at baseline used as a covariate. Pooled centers will be generated and documented prior to database lock. If the inclusion of pooled centers creates modeling problems, then dropping that factor will be considered. Subject will be identified as subject in the repeated statement. Residuals from the model will be tested for normality using the Shapiro-Wilk test; if the normality assumption is rejected then data transformations will be explored. If necessary, the model may be run on ranked values as a non-parametric alternative. An unstructrured covariance structure will be used initially, if the model fails to converge other covariance structures will be explored. The Kenward-Roger method of estimation of degrees of freedom and the restricted maximum likelihood (REML) method will be used.

Least squares (LS) means (± standard error [SE]) and 2-sided 90% CIs and p-values for the LS mean treatment differences between each dose of ASP4345 and placebo will be presented for the primary endpoint. Effect size (Cohen’s d) will also be shown, as:

$$d_s = t\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

where t is the t-value for the least squares mean pairwise difference of ASP4345 vs placebo from the MMRM model.

There will be two hypotheses tested. Hypothesis 1 is given as follows:

H_{0A}: The LS mean change from baseline at week 12 for Group A (50 mg ASP4345) and Group C (placebo) are the same

H_{1A}: The LS mean change from baseline at week 12 for Group A (50 mg ASP4345) and Group C (placebo) are not the same

Hypothesis 2 is given as follows:

H_{0B}: The LS mean change from baseline at week 12 for Group B (150 mg ASP4345) and Group C (placebo) are the same

H_{1B}: The LS mean change from baseline at week 12 for Group B (150 mg ASP4345) and Group C (placebo) are not the same

6.4.1.2 Sensitivity Analysis for Primary Efficacy Endpoint(s)

The relationship between the number of cognitive training levels, including repeat levels completed at week 12, (as a measure of compliance with cognitive training) and MCCB neurocognitive composite end of treatment scores will be evaluated using correlations overall and by treatment group.

Additionally, the primary efficacy analysis as defined in section 6.4.1.1 will be conducted using mFAS1 and mFAS2.

6.4.1.2.1 Cognitive Training

The number of training levels completed as well as the percentage of the number expected completed will be summarized. The percent of the number of training levels completed out of the number expected completed will be calculated as: [number of levels played / expected number of levels] * 100, where the expected number of training levels will increase in a step fashion, by 48 on day 1, day 7, day 14 and so on (as shown in the table below). In between 'steps', i.e. from day 1 until day 7, regardless of whether a subject completes the entire week the expected number of training levels will be constant. Additionally, training task performance will be assessed prior to the start of cognitive training (pre assessment) and again after the last cognitive training (post assessment) with a standardized task assessment (Sound Sweeps) to evaluate improvement. Pre, post and change pre to post values will be summarized.

Week	Interval	Increase in Expected Number of Training Levels at Start of Interval	Cumulative Expected Number of Training Levels
1	Day 1 to <7	48	48
2	Day 7 to <14	48	96
3	Day 14 to <21	48	144
4	Day 21 to <28	48	192
5	Day 28 to <35	48	240
6	Day 35 to <42	48	288
7	Day 42 to <49	48	336
8	Day 49 to <56	48	384
9	Day 56 to <63	48	432
10	Day 63 to <70	48	480
11	Day 70 to <77	48	528
12	Day 77 to <=84	48	576

An additional interval may be added for subjects with extended treatment periods. Incomplete intervals will be normalized to the expected interval.

6.4.1.3 Subgroup Analysis for Primary Efficacy Endpoint(s)

The primary outcome of neurocognitive MCCB score will be summarized by subgroups. The subgroups (categories) will be:

- Duration of diagnosis (>10 years, ≤ 10 years)
- Type of diagnosis (schizophrenia, schizoaffective)
- Smoking status (current, non-smoker ([including former])
- Sex (male, female)
- Cannabis use (3 groups based on laboratory results: Never positive, positive pre-dose or week 12, positive predose and week 12; where positive pre-dose is positive week 0 and/or screening)
- Compliance based on electronic mobile application (<85% compliance, ≥85% compliance)

6.4.2 Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoint of change from baseline to week 12/EoT in the UPSA-2 Extended Range instrument will be analyzed using ANCOVA, in each of the six domains and a total score. The model will contain terms for treatment group and pooled site, with the corresponding score at baseline used as a covariate.

LS means (± SE) and 2-sided 90% CIs for the LS mean treatment differences between each dose of ASP4345 and placebo will be presented as for the primary endpoint. There will be no adjustment made for multiple comparisons.

The sensitivity analysis described in 6.4.1.2 and the subgroups described in section 6.4.1.3 will also be completed for the secondary efficacy endpoint.

6.4.3 Analysis of Exploratory Endpoints

Exploratory endpoints listed below will be analyzed using the same MMRM model as the primary efficacy analysis.

- Change from baseline to week 12/EoT for NSA-16 total negative score, only for the subjects who have at least 1 negative symptom of moderate severity at baseline (a score ≥3 or ≤6 for one of the 16 symptoms assessed)
- Change from baseline to week 12/EoT for NSA-16 global negative symptoms rating
- Change from baseline to week 12/EoT for the MCCB composite T score
- Change from baseline to week 12/EoT for each of the seven MCCB domain T scores
- Change from baseline to week 12/EoT for the PANSS total score
- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the CGI-S
- The pharmacogenetics test listed below will be measured at baseline only. Genotyping data will be analyzed and reported separatelyfrom the rest of the study data.
    - Catechol-o-methyltransferase (COMT) and dopamine D_1 and D_3 receptor genotyping

The NSA-16 consists of 16 negative symptoms with scores of 0-6 for each item. Scores of 9 (not able to rate) will not be included in any continuous summary statistics. Scores for five factors (Communication, Emotion/Affect, Social Involvement, Motivation and Retardation) will be calculated. If all item have scores ≥ 0 and ≤ 6, each factor score is the sum of all the items in that factor. If there are missing items (including ratings of 9) within a factor, provided the number missing is ≤ 34% the factor score will be calculated as the sum of all items within the factor, with the missing item imputed as the average score of the observed items.

A factor score will not be calculated if the number missing is greater than 34%, and if any factor score is not calculated the total score will be not be calculated. Provided all factor scores are calculated, the total negative score will be the sum of all factor scores..

- Communication [4 items; minimum number of items to calculate factor score is 3]
    - Q1, Prolonged time to respond
    - Q2, Restricted speech quantity
    - Q3, Impoverished speech content
    - Q4, Inarticulate speech
- Emotion/Affect [3 items; minimum number of items to calculate factor score is 2]
    - Q5, Reduced range
    - Q6, Reduced modulation of intensity
    - Q7, Reduced display on demand
- Social Involvement [3 items; minimum number of items to calculate factor score is 2]
    - Q8, Reduced social drive
    - Q9, Poor rapport with interviewer

  - Q10, Interest in Emotional and Physical Intimacy
- Motivation [4 items; minimum number of items to calculate factor score is 3]
  - Q11, Poor grooming and hygiene
  - Q12, Reduced sense of purpose
  - Q13, Reduced interests
  - Q14, Reduced daily activity
- Retardation [2 items; minimum number of items to calculate factor score is 2]
  - Q15, Reduced expressive gestures
  - Q16, Slowed movements

A higher score indicates more severe symptoms. A global negative symptoms rating (a scale ranging from '1=No evidence of negative symptoms' to '7=Extremely severe negative symptoms (incapacitating)' is also assessed.

For patients who have at least one negative symptom of at least moderate severity (a score ≥ 3 or ≤ 6 for one of the 16 symptom assessments), the negative symptom burden will be further assessed with the total negative score, as calculated above. Continuous descriptive statistics for each factor score, the total negative symptom score and the global negative symptoms rating will be shown, along with the number and percentage in each category for the individual 16 symptom scores, by treatment and week.

PANSS total score is the summation of ratings across all 30 items. Traditional PANSS subscores are calculated as follows:

- Positive score: summation of ratings across 7 positive items (P1 to P7)
- Negative score: summation of ratings across 7 negative items (N1 to N7)
- General psychopathology score: summation of ratings across 16 general psychopathology items (G1 to G16).
- Composite score: positive score – negative score

In addition, five factors are calculated as follows:

- Anergia: summation of N1, N2, G7 and G10
- Thought Disturbance: summation of P2, P3, P5 and G9
- Activation: summation of P4, G4 and G5
- Paranoid / Belligerence: summation of P6, P7 and G8
- Depression: summation of G1, G2, G3 and G6

PANSS total score, sub-scores, five factors and associated changes from baseline will be listed and summarized by treatment and visit. The PANSS individual item ratings will be listed.

The Clinical Global Impression of Severity Scale (CGI-S) is a 7-point scale rating the severity of a patient's illness. Continuous descriptive statistics as well as the number and percentage in each category will be shown by treatment and week. The relationship between MCCB and CGI-S will be examined as follows:

- Correlation between MCCB and CGI-S scores at each measurement (weeks -4, -3, 0, 6, 12)
- Correlation between change from baseline to week 12/EoT in MCCB and change from baseline to week 12/EoT in CGI-S scores

6.5 Analysis of Safety

6.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent Adverse Event (TEAE) is defined as an AE observed after starting administration of the study drug and 28 days after the last dose of study drug. A study 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. There are two types of adverse events of special interest: TEAEs related to abuse, and TAEAs related to drug withdrawal. See appendix 2 for a complete list of the MedDRA preferred AE terms to be included in each AE of special interest type.

An overview table will include the following:

- 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 TEAEs leading to withdrawal of treatment
- Number and percentage of subjects with TEAEs leading to withdrawal of treatment, and
- Number of deaths
- Number of TEAEs leading to death
- Number and percentage of subjects with TEAEs leading to death
- Number of drug related TEAEs leading to death
- Number and percentage of subjects with drug related TEAEs leading to death
- Number of TEAEs of special interest related to abuse during the treatment period
- Number of TEAEs of special interest related to abuse during the follow up period
- Number of TEAEs of special interest related to drug withdrawal during the treatment period
- Number of TEAEs of special interest related to drug withdrawal during the follow up period

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

- TEAEs
- drug related TEAEs

- drug related TEAEs by severity
- drug related TEAEs leading to death
- serious TEAEs
- drug related serious TEAEs
- TEAEs by severity
- TEAEs leading to death
- TEAEs leading to withdrawal of treatment
- drug related TEAEs leading to withdrawal of treatment
- Common (>=5% in Any Treatment Group) TEAEs excluding serious adverse events
- TEAEs of special interest related to abuse during the treatment period
- TEAEs of special interest related to abuse during the follow up period
- TEAEs of special interest related to drug withdrawal during the treatment period
- TEAEs of special interest related to drug withdrawal during the follow up period

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by severity and by relationship to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity or relationship, then the subject will be counted once with the worst severity and highest degree of relationship. If any of the severity or relationship values are missing then the subject will be counted only once with missing severity or relationship.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group by time interval. For each adverse event in a particular interval, a subject will be counted if there is an onset of a treatment-emergent adverse event regardless of onset in other intervals.

Time intervals will be categorized according to the following categories:

  - 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
  - 42 days or more

Following data will be presented graphically by treatment group:
- Overview of TEAEs using dot-and-forest plot
- TEAEs by SOC using dot-and-forest plot

6.5.2 Clinical Laboratory Evaluation

The baseline value will be the last non-missing value taken on or prior to day of first dose of study drug. Quantitative values evaluated by the central laboratory including hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median by treatment group at each analysis 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 laboratory supplied reference

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

For hematology and biochemistry, a summary of shifts of reference range changes from baseline to worst finding during the treatment period will be presented for each treatment group.

The following data will be presented graphically by treatment group:

- Change from baseline in laboratory test results using box plot

6.5.2.1 Liver Safety Assessment

The liver safety assessments will be summarized by the following categories below based on the measurements from Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. These parameters will be measured from a central laboratory.

The subject's highest value during the investigational period (day of first dose and through 1 day of the last dose of study drug) will be used.

- ALT > 3xULN, > 5xULN, > 10xULN, >20xULN
- AST > 3xULN, > 5xULN, > 10xULN, >20xULN
- ALT or AST > 3xULN, > 5xULN, > 10xULN, >20xULN
- ALP > 1.5xULN
- Total Bilirubin >2xULN
- (ALT or AST > 3xULN) and Total Bilirubin > 2xULN
- (ALT or AST > 3xULN) and ALP< 2xULN and Total Bilirubin > 2xULN

The last 2 criteria where 2 or more parameters are evaluated will be with the measurements on the same day or up to a maximum of 1 day apart.

The denominator for each criterion will be the number of subjects who have at least one value during the investigational period. The number and percentage of subjects meeting the criteria during the investigational period will be summarized by treatment group.

6.5.3 Vital Signs

The baseline value will be the last non-missing value taken on or prior to day of first dose of study drug.

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized by treatment group and visit. Additionally, a within-subject change will be calculated at each visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit. Analysis visits are defined in the Analysis Windows section 6.8.1

6.5.4 Electrocardiograms

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each treatment visit and time point, including changes from baseline.

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG will be tabulated by treatment group at each treatment visit and time point.

The QTcF interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

	QTcF Interval Criteria Value (msec)
Normal	≤ 450 males; ≤ 470 females
Borderline	> 450 males; > 470 females
Prolonged	> 480 males; > 490 females
Clinically significant	> 500 males; > 500 females

The QTcF interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

Variable	**Change from Baseline**
QTcF Interval (msec)	> 30 > 60

Differences between treatments in the frequency of changes greater than 30, and greater than 60, will be evaluated with the Chi-square test at each treatment visit.

6.5.5 Metabolic Parameters

Descriptive statistics will be used to summarize individual indices of metabolic syndrome results (weight, waist circumference, cholesterol, triglycerides, HDL [the second screening visit and day 77], and fasting glucose), and hemoglobin A1c [HbA1c] and changes from baseline by treatment group and time point. Differences between treatments in change from baseline will be assessed with same MMRM model as the primary efficacy analysis, with the exception of HDL which will be analyzed using the same ANCOVA model as the secondary analysis.

6.5.6 Columbia-Suicide Severity Rating Scale

Number and percentage of subjects in each of the categories of C-SSRS, as well as changes from baseline, will be summarized by treatment group and visit.

6.5.7 Movement Disorder (Abnormal Involuntary Movement Scale)

Number and percentage of subjects in each rating category will be summarized for each of the items of the AIMS by treatment group and visit. A total score will be calculated as the sum of items 1 through 7 and descriptive statistics will be used to summarize the total score

at each visit as well as changes from baseline. Differences between treatments in the total score will be evaluated with the same MMRM model as the primary efficacy analysis.

6.5.8 Simpson Angus Scale

Number and percentage of subjects in each rating category will be summarized for each of the items of the SAS by treatment group and visit. Total scores will be calculated as the sum of each item, and categorized as [<3 (normal); 3-5 (minimal); 6-11 (clinically significant); 12-17 (severe); ≥18 (extreme)]. Descriptive statistics will be used to summarize the total score (sum) and total score (categorical) at each visit as well as changes from baseline. Differences between treatments in categorical total scores will be evaluated with a general estimating equations (GEE) model. The model will contain terms for treatment group, pooled site, visit (the repeated term), and treatment by visit, with the categorical score at baseline used as a covariate. Odds ratios comparing each active treatment and control will be assessed at week 6 and week 12.

6.5.9 Barnes Akathisia Rating Scale

Number and percentage of subjects in each of the categories of BARS will be summarized by treatment group and visit. Differences between treatments in the Global Clinical Assessment of Akathisia, scored from 0 (absent) to 5 (severe akathisia), will be evaluated with a general estimating equations (GEE) model. The model will contain terms for treatment group, pooled site, visit (the repeated term), and treatment by visit, with the Global Clinical Assessment of Akathisia score at baseline used as a covariate. Odds ratios comparing each active treatment and control will be assessed at week 6 and week 12.

6.6 Analysis of Pharmacokinetic

Descriptive statistics (e.g., N, mean, standard deviation, minimum, median, maximum, coefficient of variation [CV], geometric mean, and geometric CV) will be provided for plasma concentrations of ASP4345 and possible metabolite(s) by time point.

6.6.1 Estimation of Pharmacokinetic Parameters

Population pharmacokinetic model will be developed based on ASP4345 plasma concentration data obtained from subjects who have at least 1 pharmacokinetic sample. Population pharmacokinetics and/or pharmacokinetic/pharmacodynamics analyses will be performed by modeling and simulation scientist. All details of the population pharmacokinetic analysis will be described in a separate analysis plan and a separate population pharmacokinetic modeling report will be written.

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

There will be no interim analysis.

6.8 Additional Conventions

6.8.1 Analysis Windows

The data summary by visits will be done following the analysis windows specified in the tables below:

MCCB, NSA-16, ECG, Weight & Waist, Global Impression of Severity Scale, AIMS, BARS, and SAS Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day 1	Last non-missing value between -28 and 1 (inclusive)
Week 6	Day 42	35 to 49
Week 12	Day 84	77 to 91
Week 12/ET	Day 84	≥ 2

UPSA-2-ER Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day 1	Last non-missing value between -28 and 1 (inclusive)
Week 12	Day 84	77 to 91
Week 12/ET	Day 84	≥ 2

Vital Signs Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day 1	Last non-missing value between -28 and 1 (inclusive)
Week 1	Day 7	2 to 10
Week 2	Day 14	11 to 17
Week 3	Day 21	18 to 24
Week 4	Day 28	25 to 31
Week 5	Day 35	32 to 38
Week 6	Day 42	39 to 45
Week 7	Day 49	46 to 52
Week 8	Day 56	53 to 59
Week 9	Day 63	60 to 66
Week 10	Day 70	67 to 73
Week 11	Day 77	74 to 80
Week 12	Day 84	81 to 112
Week 12/ET	Day 84	≥ 2

Columbia-Suicide Severity Rating Scale Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day 1	Last non-missing value between -28 and 1 (inclusive)
Week 1	Day 7	2 to 10
Week 2	Day 14	11 to 17
Week 3	Day 21	18 to 24
Week 4	Day 28	25 to 31
Week 5	Day 35	32 to 38
Week 6	Day 42	39 to 45
Week 7	Day 49	46 to 52
Week 8	Day 56	53 to 59
Week 9	Day 63	60 to 66
Week 10	Day 70	67 to 73
Week 11	Day 77	74 to 80
Week 12	Day 84	81 to 112
Week 12/ET	Day 84	≥ 2
Week 14	Day 98	91 to 105

Positive and Negative Symptom Scale Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day 1	Last non-missing value between -28 and 1 (inclusive)
Week 2	Day 14	7 to 21
Week 6	Day 42	35 to 49
Week 12	Day 84	77 to 91
Week 12/ET	Day 84	≥ 2

Laboratory (Hematology, Full Biochemistry, and Urinalysis) Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day -1	Last non-missing value between -28 and 1 (inclusive)
Week 5	Day 35	28 to 42
Week 11	Day 77	70 to 84
Week 11/ET	Day 77	≥ 2
Week 14	Day 98	91 to 105

Laboratory (Abbreviated Biochemistry) Analysis Windows:

Analysis Visits	Scheduled Day in Protocol	Analysis Windows (day)
Baseline (Week 0)	Day 1	Last non-missing value between -28 and 1 (inclusive)
Week 1	Day 7	2 to 10
Week 2	Day 14	11 to 17
Week 3	Day 21	18 to 24
Week 4	Day 28	25 to 35
Week 6	Day 42	36 to 45
Week 7	Day 49	46 to 52
Week 8	Day 56	53 to 59
Week 9	Day 63	60 to 66
Week 10	Day 70	67 to 73
Week 10/ET	Day 70	≥ 2

If more than one observation exists within the analysis window, the observation closest to the scheduled visit day will be selected for that visit. If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be selected in the analysis. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

The Follow Up visit will include all data collected beyond 10 days after the last dose of study drug. If there are more than one value, then the value that is closest to day 28 from the last dose of study drug will be selected for the analysis. The same logic will be applied as in above for more than one value.

6.8.2 Imputation Rules for Incomplete Dates

In case of missing partial start and stop dates for concomitant medications, the following rules will be used:

If the start date is missing or partial:

- if the month is missing, use January
- if the day is missing, use the first day of the month under consideration
- if the year is missing, use year of the informed consent date
- if the entire date is missing, use informed consent date

If the stop date is missing or partial:

- if the month is missing, use December
- if the day is missing, use the last day of the month under consideration
- if the year or the entire date is missing, set the stop date to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.

For AEs, a missing or incomplete onset date will be imputed according to the following conventions.

If an onset date is missing or only the year is known, the imputed onset date will be the date of first dose of study drug.

If only the year is known for the AE onset date, the imputed onset date will be the latest of the following non-missing dates:

- Date of first dose of study drug
- January 1 of the year of AE onset date

If only the month and year is known for the onset date, set the surrogate onset date to the first day of that month and then apply the following rules.

- If the month and year of the onset date is prior to the month and year of the first dose of study drug, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of study drug, then the imputed onset date will be the **latest** of the following non-missing dates:
    - Date of first dose of study drug
    - Surrogate onset date

If the imputed onset date is after the adverse event end date, the imputed onset date will be the same as the adverse event end date.

7 REVISION AND RATIONALE

8 REFERENCES

Calulating and reporting effect sizes to facitiltate cumulative science: a practical primer for t-tests and ANOVAs. Lakens, Daniel, *Frontiers in Psychology* November 2013 Vol 4 Article 863.

9 APPENDICES

9.1 Appendix 1: Author and Approver Signatures

Prepared by: _____ Date: _____

PPD

Date (DD Mmm YYYY)

Approved by: _____ Date: _____

PPD

Date (DD Mmm YYYY)

Approved by: _____ Date: _____

PPD

Date (DD Mmm YYYY)

9.2 Appendix 2: Adverse Events of Special Interest (Preferred Terms; MedDRA 18.0)

9.2.1 Adverse Events of Interest Related to Abuse requiring narratives

Euphoria-related Terms

Preferred term	Lowest level term
Euphoric mood	Feeling high
Elevated mood	
Feeling abnormal	
Feeling drunk	
Feeling of relaxation	
Thinking abnormal	
Hallucination, mixed	
Inappropriate affect	
	Dizziness and giddiness

Dissociative/Psychotic Terms

Preferred term	Lowest level term
Psychosis acute	Psychosis
Aggression	
	Confusion and disorientation

Terms Indicative of Impaired Attention, Cognition, Mood, and Psychomotor Events

Preferred term	Lowest level term
Somnolence	
Psychomotor hyperactivity/decreased activity	Hyperactivity/hypoactivity
	Mood disorders and disturbances
	Mental impairment disorders
	Drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders

Inappropriate Affect

Preferred term	Lowest level term
Inappropriate affect	Elation inappropriate
	Exhilaration inappropriate
	Inappropriate mood elevation
Product tampering	Medication tampering

9.2.2 Drug Abuse – Related Adverse Events

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lower Level Term
Psychiatric disorders	Mood disorders and disturbances NEC	Emotional and mood disturbances NEC	Euphoric Mood	Euphoria
				Euphoric
				Euphoric mood
				Exaggerated well-being
				Feeling high
				Felt high
				High
				High feeling
				Laughter
			Mood altered	Affect alteration
				Affect altered
				Altered mood
				Bad mood
				Mood alteration NOS
				Mood altered
				Mood change
			Elevated mood	Elevated mood
				Mood elevated
		Affect alterations	Inappropriate affect	Elation inappropriate
				Exhilaration inappropriate
				Exhiliration inappropriate
				Feeling happy inappropriately
				Inappropriate affect
				Inappropriate crying
				Inappropriate elation
				Inappropriate exhilaration
				Inappropriate laughter
				Inappropriate mood elevation
				Mood elevation inappropriate
	Disturbances in thinking	Perception disturbances	Hallucination	Drug-induced hallucinosis

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lower Level Term
	and perception			Hallucinating
				Hallucination
				Hallucination NOS
				Hallucinations
				Hallucinations aggravated
				Kinesthetic hallucination
				Organic hallucinosis syndrome
				Pseudohallucination
				Sensory hallucinations
				Stump hallucination
			Hallucination, auditory	Auditory hallucinations
				Hallucination auditory
				Hallucination, auditory
				Verbal hallucinations
			Hallucination, visual	Hallucination visual
				Hallucination with color
				Hallucination with colour
				Hallucination, visual
				Visual hallucinations
General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	Feeling drunk	Drunk-like effect
				Drunkenness feeling of
				Feeling drunk
			Feeling abnormal	Cotton wool in head
				Feeling abnormal
				Feeling bad
				Feeling dazed
				Feeling floating
				Feeling lifeless
				Feeling miserable
				Feeling stoned
				Feeling strange

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lower Level Term
				Feeling weightless
				Feels awful
				Feels bad
				Feels poorly
				Felt like a zombie
				Floating feeling
				Foggy feeling head
				Funny episode
				Fuzzy
				Fuzzy head
				Muzzy head
				Neck strange feeling of
				Soft feeling
				Spaced out
				Thick head
				Unstable feeling
				Weird feeling

9.2.3 Drug Withdrawal – Related Adverse Events

	Higher Level GT	Higher Level Term	Preferred Term
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Agitation
Nervous system disorders	Neurological disorders NEC	Neurological signs and symptoms NEC	
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Anhedonia
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Anxiety
Musculoskeletal and connective tissue disorders	Muscle disorders	Muscle related signs and symptoms NEC	Chills
Musculoskeletal and connective tissue disorders	Muscle disorders	Feelings and sensations NEC	
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Depressed mood
Psychiatric disorders	Depressed mood disorders and disturbances	Depressive disorders	Depression
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (excl infective)	Diarrhoea
Psychiatric disorders	Mood disorders and disturbances	Emotional and mood disturbances NEC	Dysphoria
Nervous system disorders	Sleep disturbances (incl subtypes)	Sleep disturbances NEC	Dyssomnia
Psychiatric disorders	Sleep disorders and disturbances	Dyssomnias	
Psychiatric disorders	Depressed mood disorders and disturbances	Depressive disorders	Dysthymic disorder
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Feeling of despair
Nervous system disorders	Headaches	Headaches NEC	Headache
Skin and subcutaneous tissue disorders	Skin appendage conditions	Apocrine and eccrine gland disorders	Hyperhidrosis
General disorders and administration	General system disorders NEC	General signs and symptoms NEC	

	Higher Level GT	**Higher Level Term**	**Preferred Term**
site conditions			
Psychiatric disorders	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Insomnia
Nervous system disorders	Sleep disturbances	Disturbances in initiating and maintaining sleep	
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Morose
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Nausea
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Negative thoughts
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Nervousness
Psychiatric disorders	Anxiety disorders and symptoms	Obsessive-compulsive disorders and symptoms	Obsessive thoughts
General disorders and administration site conditions	General system disorders NEC	Pain and discomfort NEC	Pain
Nervous system disorders	Sleep disturbances (incl subtypes)	Sleep disturbances NEC	Poor quality sleep
Psychiatric disorders	Sleep disorders and disturbances	Dyssomnias	
Cardiac disorders	Cardiac disorder signs and symptoms	Cardiac signs and symptoms NEC	Syncope
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Circulatory collapse and shock	
Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	
Psychiatric disorders	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Terminal insomnia (lower level term of interest: early morning awakening)
Nervous system disorders	Sleep disturbances	Disturbances in initiating and maintaining sleep	
Nervous system disorders	Movement disorders (incl parkinsonism)	Tremor (excl congenital)	Tremor
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Vomiting