STATISTICAL ANALYSIS PLAN

A multicenter, uncontrolled, open-label trial to evaluate the safety of extended treatment with brexpiprazole (OPC-34712) in patients with agitation associated with dementia of the Alzheimer's type

NCT Number: NCT03724942
Protocol No. 331-102-00184
Version Date: 04 Feb 2022 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug Brexpiprazole (OPC-34712)

Protocol No. 331-102-00184

A multicenter, uncontrolled, open-label trial to evaluate the safety of extended treatment with brexpiprazole (OPC-34712) in patients with agitation associated with dementia of the Alzheimer's type

Statistical Analysis Plan

Version: 1.0
Date: 04 Feb 2022
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BUN	Blood urea nitrogen
CGI-I	Clinical Global Impression - Global Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CMAI	Cohen-Mansfield Agitation Inventory
CPK	Creatine phosphokinase
DIEPSS	Drug Induced Extra-Pyramidal Symptoms Scale
FAS	Full analysis set
HDL	High-density lipoprotein
IDMC	Independent data monitoring committee
LDH	Lactate (lactic acid) dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
[redacted]	[redacted]
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate by Bazett's formula
QTcF	QT corrected for heart rate by Fridericia's formula
QTcN	QT corrected for heart rate by FDA Neuropharmacological Division formula
S-STS	Sheehan Suicidality Tracking Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limits of normal

1 Introduction

This statistical analysis plan documents in detail the statistical analysis methods planned for the clinical study report of Trial 331-102-00184.

2 Trial Objectives

The objective of the trial is to evaluate the safety of brexpiprazole 1 or 2 mg administered for 14 weeks in patients with agitation associated with dementia of Alzheimer's type who have completed the treatment period of a double-blind trial (Trial 331-102-00088), and to explore the efficacy of extended treatment with brexpiprazole.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, uncontrolled, open-label trial to evaluate the efficacy and safety of brexpiprazole in patients with agitation associated with dementia of the Alzheimer's type who require medication. The overview of the trial design is shown in Figure 3.1-1.

The trial consists of a screening period, a treatment period, and a follow-up period. The investigator or subinvestigator will explain the details of the trial to prospective subjects (if the investigator or subinvestigator judges that the subject is incapable of providing informed consent, or if the subject is hospitalized for reasons related to medical protection, the subject's legally acceptable representative must provide written consent, and even when written consent is obtained from the legally acceptable representative, the subject should be given an explanation appropriate to his or her level of understanding and, if possible, should also provide written consent) and their main caregivers using the explanatory materials and informed consent form (ICF) and obtain written consent for participation in the trial from the prospective subjects (or their legally acceptable representatives) and caregivers during Trial 331-102-00088 between the dates of evaluation at Week 4 and Week 10. The investigator or subinvestigator will assess the eligibility of subjects to participate in the trial based on observations, tests, and investigations performed during the treatment period of Trial 331-102-00088. All subjects judged to be eligible based on the results of observations, tests, and investigations in Trial 331-102-00088 will skip the follow-up observation of Trial 331-102-00088 and be rolled over into the treatment period of this trial (331-102-00184). Subjects will receive brexpiprazole for 14 weeks, starting at 0.5 mg, followed by dose titration, and then at either 1 or 2 mg, according to Section 3.2 Trial Treatments, and will undergo periodic observation, tests, and investigations to assess efficacy and safety. Investigational medicinal product (IMP) administration will begin no later than 10 days

after the date of evaluation at Week 10 of Trial 331-102-00088. The subject will return to the trial site 28 days after the completion of IMP administration for follow-up observation. Discontinued subjects will also undergo follow-up observation.

For subjects who discontinued the trial during the treatment period, the examination at discontinuation will be performed.

The trial period for each subject is from completion of evaluation at Week 10 of Trial 331-102-00088 to the end of follow-up observation.

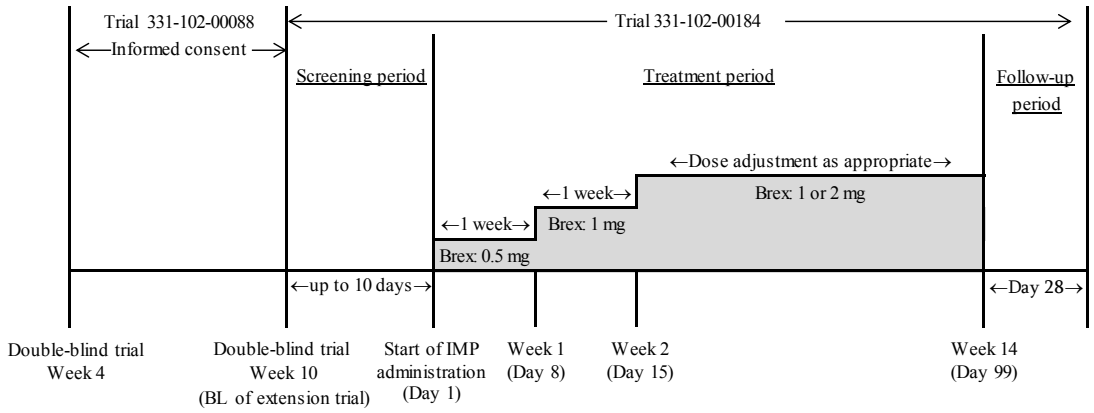

Figure 3.1-1 Trial Design

Double-blind trial = Trial 331-102-00088, Extension trial = Trial 331-102-00184, Brex = brexpiprazole, BL = baseline

3.2 Trial Treatments

Brexpiprazole will be administered orally as one tablet once a day for 14 weeks. Although the temporal relationship between IMP administration and meals will not be considered, subjects should take the IMP at the specified time in so far as possible. The IMP doses are shown in Table 3.2-1. IMP administration will be initiated at 0.5 mg and the dose will be increased to 1 mg after evaluation at Week 1 (Day 8) and to 2 mg after evaluation at Week 2 (Day 15). If the investigator or subinvestigator judges that dose increase to 2 mg is difficult for safety reasons based on the subject's condition after evaluation at Week 2 (Day 15), the dose may be maintained at 1 mg (see Section 3.2 1) Dose Maintenance at 1 mg). From Week 2 (Day 15), the dose may be reduced or increased to 1 or 2 mg if the investigator or subinvestigator decides that dose adjustment is necessary (see Section 3.2 2) Dose Change). In cases where dose reduction to lower than 1 mg is required, the trial should be discontinued.

Table 3.2-1 Doses of IMP		
Day 1-7	Day 8-14	Day 15-98
0.5 mg	1 mg	1 mg or 2 mg

1) Dose Maintenance at 1 mg

   If the investigator or subinvestigator decides that dose increase to 2 mg is difficult due to the occurrence of an adverse event (AE) identified from the evaluation at Week 2 (Day 15), the dose will be maintained at 1 mg. The AE for which this judgement was made will be recorded in the case report form (CRF).

2) Dose Change

   If the investigator or subinvestigator decides that dose adjustment is necessary based on the subject's condition, the dose will be reduced or increased to 1 or 2 mg.

   If the investigator or subinvestigator decides that the current dose is not sufficiently effective, the dose will be increased to 2 mg. If either of the following cases applies, the dose will be reduced to 1 mg and the reason for dose reduction will be recorded in the CRF. In the event that both of the following cases apply, the AE should be recorded as the reason for dose reduction. When the occurrence of an AE necessitates dose reduction, enter "dose reduction" in the CRF as the action taken for the AE in relation to IMP administration.

   The dose may be reduced to 1 mg in the following cases:

   – Dose reduction is necessary because an AE has occurred.
   – Dose reduction is necessary because symptoms have improved.

3.3 Trial Population

A total of 157 male and female patients with agitation associated with dementia of the Alzheimer's type who have completed the treatment period of Trial 331-102-00088 and whose condition can be observed by a caregiver in at least 4 days per week for 4 hours or more a day.

3.4 Trial Visit Window

For all endpoints, acceptable windows for analysis are specified, and analysis should take place at the analysis time points regardless of time points recorded on the case report form.

Acceptable windows for analysis are shown in Table 3.4-1. Day 1 is defined as the day when treatment with the IMP begins. If multiple data exist within an acceptable window, the last data within the window will be used in analysis. Data obtained 7 days or later after the final dosing will be excluded from the analysis.

Table 3.4-1 Acceptable Windows for Analysis		
Week	**Target Day**	**Trial Day Interval**
Baseline	1	- 1
Week 1	8	2 - 11
Week 2	15	12 - 22
Week 4	29	23 - 36
Week 6	43	37 - 50
Week 8	57	51 - 64
Week 10	71	65 - 78
Week 12	85	79 - 92
Week 14	99	93 - 113

3.5 Handling of Endpoints

3.5.1 Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI total score will be the sum of scores for 29 CMAI items.

The CMAI Aggressive Behavior score will be the sum of scores for CMAI Items 3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 21, and 25.

The CMAI Physically Non-aggressive Behavior score will be the sum of scores for CMAI Items 1, 2, 16, 22, 26, and 29.

The CMAI Verbally Agitated Behavior score will be the sum of scores for CMAI Items 5, 6, 18, and 19.

3.5.2 Clinical Global Impression - Severity of Illness (CGI-S)

"0. Not assessed" will be handled as missing data.

3.5.3 Clinical Global Impression - Improvement (CGI-I)

"0. Not assessed" will be handled as missing data.

3.5.4 [redacted]

[redacted]

3.5.5 [redacted]

[redacted]

3.5.6 Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS)

The DIEPSS total score will be the sum of scores for DIEPSS items 1 through 8.

3.5.7 Abnormal Involuntary Movement Scale (AIMS)

The AIMS total score will be the sum of scores for AIMS items 1 through 7.

3.5.8 Sheehan Suicidality Tracking Scale (S-STS)

The S-STS total score will be the sum of scores for Item 1a, Items 2 through 11, highest of Item 12 or any row of Item 16, highest of Item 14 or any row of Item 15, Item 17, and Item 20.

The S-STS suicidal ideation subscale score will be the sum of scores for Items 2 through 11.

The S-STS suicidal behavior subscale score will be the sum of scores for Item 1a, highest of Item 12 or any row of Item 16, highest of Item 14 or any row of Item 15, Item 17, and Item 20.

3.5.9 Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

The ADCS-ADL total score will be the sum of scores for ADCS-ADL Items 1 through 19.

3.5.10 Mini-Mental State Examination (MMSE)

The MMSE total score will be the sum of scores for MMSE Items 1 through 30.

4 Sample Size

This trial aims to include 100 completers of brexpiprazole treatment in Trial 331-102-00088 as subjects who will continue to receive brexpiprazole for more than 10 weeks. Since patients are assigned to the 1 mg group, the 2 mg group, or the placebo group at a ratio of 3:4:4 in Trial 331-102-00088, the target sample size for this trial (331-102-

00184) has been determined to be 157 subjects, taking into account some of them have received placebo in the previous trial.

5 Statistical Analysis Datasets

Analyses in this trial will be performed for each of the following groups unless otherwise specified:

- Rollover subjects from the brexpiprazole group in Trial 331-102-00088
- Rollover subjects from the placebo group in Trial 331-102-00088
- All subjects (rollover subjects from the brexpiprazole group + rollover subjects from the placebo group)

5.1 Efficacy Analysis Set

The efficacy analysis set will comprise subjects who have received at least 1 dose of the IMP and from whom CMAI total scores have been obtained at baseline and at least 1 time point after initiation of treatment.

5.2 Safety Analysis Set

The safety analysis set will comprise subjects who have received at least 1 dose of the IMP.

5.3 Handling of Missing Data

For analyses at the final assessment, the last observation carried forward (LOCF) method (in which missing Week 14 data are imputed by the data which were observed after initiation of IMP treatment and obtained immediately before Week 14) will also be used.

6 Primary and Secondary Outcome Variables

Neither primary nor secondary outcome variables are planned.

7 Disposition and Demographic Analysis

7.1 Subject Disposition

Numbers and proportions of subjects from whom informed consent was obtained, those who received trial treatment, those who completed the trial, those who discontinued the trial, those who discontinued the trial by reason for discontinuation, and those included in each analysis set will be summarized.

7.2 Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, minimum, median, and maximum; hereinafter the same applies) of age, height,[a] baseline body weight, and baseline body mass index (BMI), and frequency distribution of age category (< 80, ≥ 80) (< 65, ≥ 65 to < 75, ≥ 75), sex,[a] race,[a] ethnicity,[a] country where trial is conducted,[a] complications,[a] medical history,[a] and dose used in the previous trial will be determined in each analysis set.

[a]Data obtained at screening in Trial 331-102-00088 will be used.

7.3 Baseline Disease Evaluation

Descriptive statistics of the duration of dementia of the Alzheimer's type,[a] duration of agitation associated with dementia of the Alzheimer's type,[a] [redacted] CGI-S, CMAI (total score, subscale scores), MMSE total score, and ADCS-ADL total score, and frequency distribution of medical care category,[b] prior use of antipsychotics (yes or no),[a] type of caregiver,[b] and concomitant use of antidementia drugs (yes or no).

[a]Data obtained at screening in Trial 331-102-00088 will be used.
[b]Data obtained at the start of the present trial will be used.

The duration of dementia of the Alzheimer's type and the duration of agitation associated with dementia of the Alzheimer's type will be calculated using the following formula: duration (months) = (date of subject demographic evaluation – date of onset + 1) / 30. Any unknown month or day of onset will be replaced with June or 15, respectively.

7.4 Treatment Compliance

Treatment compliance (number of days when the subject actually received the IMP/number of days for which the IMP was prescribed) will be grouped into < 70%, ≥ 70% to < 80%, ≥ 80% to < 90%, and ≥ 90%, and the frequency distribution will be determined in the efficacy analysis set.

7.5 Prior and Concomitant Medications

Numbers and proportions of subjects who used medications before, during, and after the treatment period will be determined by drug class and preferred term of the World Health Organization Drug Dictionary (WHODD) version Global B3 March 2018 in the safety analysis set.

7.6 Protocol Deviations

Numbers and proportions of subjects with major deviations from the protocol will be determined for each category (IMP administration, eligibility criteria, a failure to discontinue the trial when the subject meets the withdrawal criteria, procedures that affect evaluation of the primary endpoint, use of prohibited medications, and overall) at each trial site in the safety analysis set.

8 Efficacy Analysis

Efficacy analyses will be performed on the efficacy analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in this trial.

- CMAI total score
- CMAI subscales (Aggressive Behavior, Physically Non-aggressive Behavior, and Verbally Agitated Behavior)
- CGI-S
- CGI-I

For endpoints other than CGI-I, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated. For CGI-I, descriptive statistics of actual measurements at each time point and the final assessment (Week 14 LOCF) will be calculated.

[redacted].

8.1 Subgroup Analyses

No subgroup efficacy analyses will be performed.

9 Safety Analyses

Safety analysis will be performed using the safety analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in this trial.

9.1 Extent of Exposure

Descriptive statistics and frequency distribution (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, 50-56, 57-63, 64-70, 71-77, 78-84, 85-91, 92-98, > 98, and ≥ 7, ≥ 14, ≥ 28, ≥ 42, ≥ 56, ≥ 70, ≥ 84, ≥ 98) of the duration (days) of treatment with the IMP will be determined.

Descriptive statistics of the mean daily dose will be determined for each section of the treatment period (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, 50-56, 57-63, 64-70, 71-77, 78-84, 85-91, 92-98, > 98) and for the entire treatment period.

Frequency distribution of the most frequent dose will be determined for each section of the treatment period (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, 50-56, 57-63, 64-70, 71-77, 78-84, 85-91, 92-98, > 98) and for the entire treatment period. Frequency distribution of the final dose will also be determined.

9.2 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (Ver. 25.0). The incidences of the following events will be summarized according to System Organ Class (SOC) and Preferred Term (PT). If an AE occurs more than once in the same subject, the severest event will be used in summarization.

- Adverse events occurring after initiation of IMP administration (treatment-emergent adverse events [TEAEs])
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs leading to IMP dose reduction
- TEAEs occurring in ≥ 2% of subjects in any group

- TEAEs by days of initial onset (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, 50-56, 57-63, 64-70, 71-77, 78-84, 85-91, 92-98, > 98, post-trial treatment).

TEAEs potentially causally related to the IMP will also be summarized in the same manner.

9.2.1 Adverse Events of Interest

Each AE of interest is defined in Appendix 4 in the Statistical Analysis Plan for the double-blind trial (331-102-00088). Numbers and proportions of subjects with the following AEs of interest will be summarized by SOC and PT.

- Extrapyramidal AEs
- Accident- and injury-related AEs
- Cerebrovascular AEs
- Cardiovascular AEs
- Glucose metabolism-related AEs
- Lipid metabolism-related AEs
- Body weight-related AEs
- Blood disorder-related AEs
- Hypersensitive symptom-related AEs
- Neuroleptic malignant syndrome-related AEs
- Orthostatic disorder-related AEs
- Prolactin increase-related AEs
- QT interval prolongation-related AEs
- Rhabdomyolysis
- Seizure-related AEs
- Oversedation-related AEs
- Suicide/suicide attempt-related AEs
- Venous thrombosis
- Infectious pneumonia

9.2.2 Subgroup Analysis of Adverse Events

Numbers and proportions of subjects with TEAEs will be summarized by SOC and PT in each of the following subgroups. Subgroups of medical care category and subgroups of type of caregiver will include only subjects for whom the medical care category or the type of caregiver remains unchanged throughout the trial.

- Medical care category (inpatient, outpatient)

- Prior use of antipsychotics (yes or no)
- Type of caregiver (hospital staff, care facility staff, family, or other)
- Sex (male, female)
- Age (< 80, ≥ 80) (< 65, ≥ 65 to < 75, ≥ 75)
- Body weight (≤ median, > median)
- BMI (≤ median, > median)
- Impact of COVID-19 pandemic (subjects who completed/discontinued the trial before 07 Apr 2020, subjects who completed/discontinued the trial on or after 07 Apr 2020)
- Concomitant use of antidementia drugs (yes or no)

9.3 Clinical Laboratory Data

For each quantitative laboratory parameter, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

For each quantitative laboratory parameter, actual measurements will be classified as "lower than the lower limit of the reference range," "within the reference range," and "higher than the upper limit of the reference range" using the reference range specified by the central laboratory, and a shift table from baseline will be produced.

For each qualitative laboratory parameter, a shift table from baseline will be produced.

Numbers and proportions of subjects with laboratory test values not meeting the criteria for potentially clinically significant laboratory test values (Appendix 2) at baseline and meeting the criteria after treatment will be determined. A listing of these subjects will be provided.

Numbers and proportions of subjects with postdose values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBL) meeting Hy's Law criteria (ALT or AST ≥ 3 × the upper limit of normal [ULN] and TBL ≥ 2 × ULN) will be determined. A listing of these subjects will be provided.

Numbers and proportions of subjects with a prolactin value not meeting the criteria of > 1 × ULN, > 2 × ULN, or > 3 × ULN at baseline and meeting the criteria after treatment will be determined by sex. A listing of these subjects will be provided.

Numbers and proportions of subjects with postdose values of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and blood glucose meeting the criteria for changes in glucose and lipid metabolism-related parameters (Table 9.3-1) will be determined by baseline value. A listing of these subjects will be provided.

Table 9.3-1 Changes in Glucose and Lipid Metabolism-related Parameters		
LAB PARAMETER	**BASELINE**	**ANYTIME POST BASELINE**
Cholesterol, Fasting (mg/dL)	Normal <200 Borderline 200-<240 Normal/Borderline <240 Normal <200 Any Value	High >=240 High >=240 High >=240 Borderline/High >=200 Increased >=40
LDL Cholesterol, Fasting (mg/dL)	Normal <100 Borderline 100-<160 Normal/Borderline <160 Normal <100 Any Value	High >=160 High >=160 High >=160 Borderline/High >=100 Increased >=30
HDL Cholesterol, Fasting (mg/dL)	Normal >=40 Any Value	Low <40 Decreased >=20
Triglycerides, Fasting (mg/dL)	Normal <150 Normal <150 Borderline 150-<200 Normal/Borderline <200 Normal/Borderline <200 Normal <150 Normal/Borderline/high <500 Any Value	High 200-<500 Very High >=500 High 200-<500 High 200-<500 Very High >=500 Borderline/High/Very High >=150 Very High >=500 Increased >=50
Glucose Fasting, Serum (mg/dL)	Normal <100 Impaired 100-<126 Normal/Impaired <126 Any Value	High >=126 High >=126 High >=126 Increased >=10

9.4 Vital Sign Data

For each vital sign parameter (sitting position), descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

Numbers and proportions of subjects with vital signs meeting the criteria for potentially clinically significant vital signs (Appendix 1) will be determined. A listing of these subjects will be provided.

9.5 Physical Examination Data

Physical examination data will be provided in a listing.

9.6 Electrocardiogram Data

For heart rate, PR interval, RR interval, QRS interval, QT interval, and QT corrected for heart rate (QTc), descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

A shift table from baseline for normal/abnormal 12-lead electrocardiogram (ECG) (evaluated at the trial site) will be produced.

Numbers and proportions of subjects with actual measurements of QTc [QTcF, QTcB, QTcN = QT interval/(RR interval)$^{0.37}$] not meeting the criteria of > 450 msec, > 480 msec, or > 500 msec at baseline and meeting the criteria after treatment will be determined. Numbers and proportions of subjects with changes from baseline of > 30 msec and > 60 msec will be determined. Numbers and proportions of subjects with actual measurements of > 450 msec with a % change from baseline of > 10% will be determined.

Numbers and proportions of subjects with ECG results meeting the criteria for potentially clinically significant ECG data (Appendix 3) will be determined. A listing of these subjects will be provided.

9.7 Other Safety Data

9.7.1 Body Weight and BMI

For body weight and BMI, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

Numbers and proportions of subjects with results meeting the criteria for potentially clinically significant body weight gain or loss (Appendix 1) will be determined. Body weight data will also be analyzed by baseline BMI category (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30) in a similar manner. A listing of subjects with results meeting the criteria for potentially clinically significant body weight gain or loss (Appendix 1) will be provided.

9.7.2 DIEPSS, AIMS, and BARS

For DIEPSS total score (total of scores for items 1 through 8) and score for each DIEPSS item, AIMS total score (total of scores for items 1 through 7) and score for each of the 3 global judgment items (items 8 through 10), and BARS, descriptive statistics of actual measurements and changes from baseline at each time point and the last assessment time point (Week 14 LOCF) and the worst postdose measurement and its change from baseline will be calculated.

9.7.3 S-STS

For the score for each S-STS item (2 through 14), total score, suicidal ideation subscale score, and suicidal behavior subscale score, descriptive statistics of actual measurements

and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

10 Pharmacokinetic Analyses

Not applicable.

11 Pharmacodynamic Analyses

Not applicable.

12 Pharmacogenomic Analyses

Not applicable.

13 Analysis of Other Endpoints

Analysis of other endpoints will be performed using the safety analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment.

- ADCS-ADL
- MMSE

For ADCS-ADL total score and MMSE total score, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

14 Interim Analysis

In this trial, safety will also be evaluated by the IDMC, when approximately 25%, 50%, and 75% of the target number of subjects in the preceding Trial 331-102-00088 have completed or discontinued the trial. Additional evaluation by the IDMC may be performed depending on the status of subject enrollment into the current trial (331-102-00184).

A statistical analysis plan for interim analysis is described in a separate interim analysis plan.

15 Changes in the Planned Analyses

[redacted]

[redacted]

The following changes were made to categorical analyses of QTc:

- Only subjects with postdose QTc meeting the criteria will be summarized, instead of summarization at all time points.
- Only subjects with QTc not meeting the criteria at baseline and meeting the criteria after baseline will be summarized.

16 References

Not applicable.

Appendix 1 Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Pulse Rate	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Weight	-	≥ 7% increase ≥ 7% decrease

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Endocrinology	
Prolactin	> ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,000/ mm^3
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, Fasting	≥ 150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate	≥ 120 bpm ≤ 50 bpm	increase of ≥ 15 bpm decrease of ≥ 15 bpm
PR	≥ 200 msec	increase of ≥ 50 msec
QRS	≥ 120 msec	increase of ≥ 20 msec
QTcF	> 450 msec (males) > 470 msec (females)	

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 4 List of Summary Tables

CT-1	Subject Disposition (Enrolled Subjects)
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CT-5.4.1	Summary of Mean CGI-I Score (Efficacy Analysis Set)
[redacted]	[redacted]
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CT-7.2	Duration of Exposure Summary (Safety Analysis Set)
CT-7.3	Summary of Average Daily Dose (mg) (Safety Analysis Set)
CT-7.4	Summary of Modal and Final Dose (Safety Analysis Set)
CT-7.5	Summary of Treatment Compliance (Efficacy Analysis Set)
CT-8.1	Adverse Events (All Causalities) (Safety Analysis Set)

CT-8.2.1	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.2.2	Incidence of Drug-related TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.3.1	Incidence of TEAEs by MedDRA System Organ Class, Preferred Term and Severity (Safety Analysis Set)
CT-8.3.2	Incidence of Drug-related TEAEs by MedDRA System Organ Class, Preferred Term and Severity (Safety Analysis Set)
CT-8.4.1	Incidence of Deaths due to TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.4.2	Incidence of Deaths due to Drug-related TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.5.1	Incidence of Serious TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.5.2	Incidence of Serious Drug-related TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.6.1	Incidence of TEAEs Resulting in Discontinuation of IMP by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.6.2	Incidence of Drug-related TEAEs Resulting in Discontinuation of IMP by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.7.1	Incidence of TEAEs Resulting in Dose Reduction of IMP by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.7.2	Incidence of Drug-related TEAEs Resulting in Dose Reduction of IMP by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.8.1	Incidence of TEAEs of at Least 2% in Any Group by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.8.2	Incidence of Drug-related TEAEs of at Least 2% in Any Group by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.9.1	Incidence of TEAEs by MedDRA System Organ Class, Preferred Term and Time to First Onset (Safety Analysis Set)
CT-8.9.2	Incidence of Drug-related TEAEs by MedDRA System Organ Class, Preferred Term and Time to First Onset (Safety Analysis Set)
CT-8.10.1	Incidence of TEAEs for EPS (Safety Analysis Set)
CT-8.10.2	Incidence of TEAEs for Accidents and Injuries Including Fall (Safety Analysis Set)
CT-8.10.3	Incidence of TEAEs for Cerebrovascular Events (Safety Analysis Set)
CT-8.10.4	Incidence of TEAEs for Cardiovascular Events (Safety Analysis Set)
CT-8.10.5	Incidence of TEAEs for Effect on Glucose (Safety Analysis Set)
CT-8.10.6	Incidence of TEAEs for Effect on Lipids (Safety Analysis Set)
CT-8.10.7	Incidence of TEAEs for Effect on Weight (Safety Analysis Set)
CT-8.10.8	Incidence of TEAEs for Haematopoietic/Leukopenia (Safety Analysis Set)
CT-8.10.9	Incidence of TEAEs for Hypersensitivity (Safety Analysis Set)
CT-8.10.10	Incidence of TEAEs for Neuroleptic Malignant Syndrome (Safety Analysis Set)
CT-8.10.11	Incidence of TEAEs for Orthostatic Hypotension, Dizziness, and Syncope (Safety Analysis Set)
CT-8.10.12	Incidence of TEAEs for Effect on Prolactin (Safety Analysis Set)
CT-8.10.13	Incidence of TEAEs for QT Prolongation (Safety Analysis Set)
CT-8.10.14	Incidence of TEAEs for Rhabdomyolysis and CPK Elevation (Safety Analysis Set)
CT-8.10.15	Incidence of TEAEs for Seizures (Safety Analysis Set)
CT-8.10.16	Incidence of TEAEs for Somnolence (Safety Analysis Set)
CT-8.10.17	Incidence of TEAEs for Suicidality (Safety Analysis Set)
CT-8.10.18	Incidence of TEAEs for VTE (Thrombotic and Embolic Events) (Safety Analysis Set)
CT-8.10.19	Incidence of TEAEs for Infective Pneumonia (Safety Analysis Set)

CT-8.11.1	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Medical Care Category (Safety Analysis Set)
CT-8.11.2	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Prior Antipsychotics (Safety Analysis Set)
CT-8.11.3	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Main Care Giver (Safety Analysis Set)
CT-8.11.4	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Gender (Safety Analysis Set)
CT-8.11.5.1	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Age(< 80, >= 80) (Safety Analysis Set)
CT-8.11.5.2	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Age(<65, >=65 - <75, >=75) (Safety Analysis Set)
CT-8.11.6	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Baseline Weight (Safety Analysis Set)
CT-8.11.7	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Baseline BMI (Safety Analysis Set)
CT-8.11.8	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Impact of COVID-19 Pandemic (Safety Analysis Set)
CT-8.11.9	Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Concomitant Antidementia Drugs (Safety Analysis Set)
CT-9.1	Listing of Deaths (Safety Analysis Set)
CT-9.2	Listing of Serious Adverse Events (Safety Analysis Set)
CT-9.3	Listing of Discontinuation of IMP due to Adverse Events (Safety Analysis Set)
CT-9.4	Listing of Dose Reduction due to Adverse Events (Safety Analysis Set)
CT-10.1.1	Mean Change From Baseline in Clinical Laboratory Test Results - Serum Chemistry (Safety Analysis Set)
CT-10.1.2	Mean Change From Baseline in Clinical Laboratory Test Results - Hematology (Safety Analysis Set)
CT-10.1.3	Mean Change From Baseline in Clinical Laboratory Test Results - Urinalysis (Safety Analysis Set)
CT-10.1.4	Mean Change From Baseline in Clinical Laboratory Test Results - Prolactin, by Gender (Safety Analysis Set)
CT-10.1.5	Mean Change From Baseline in Clinical Laboratory Test Results - Other Tests (Safety Analysis Set)
CT-10.2.1	Shift Tables of Clinical Laboratory Test Results - Serum Chemistry (Safety Analysis Set)
CT-10.2.2	Shift Tables of Clinical Laboratory Test Results - Hematology (Safety Analysis Set)
CT-10.2.3	Shift Tables of Clinical Laboratory Test Results - Urinalysis1 (Safety Analysis Set)
CT-10.2.4	Shift Tables of Clinical Laboratory Test Results - Urinalysis2 (Safety Analysis Set)
CT-10.2.5	Shift Tables of Clinical Laboratory Test Results - Prolactin, by Gender (Safety Analysis Set)
CT-10.2.6	Shift Tables of Clinical Laboratory Test Results - Other Tests (Safety Analysis Set)
CT-10.3.1	Incidence of Laboratory Test Values With Potential Clinical Relevance (Safety Analysis Set)
CT-10.3.2	Listing of Laboratory Test Values With Potential Clinical Relevance by Subject (Safety Analysis Set)
CT-10.4.1	Incidence of Potential Hy's Law Cases (Safety Analysis Set)
CT-10.4.2	Listing of Potential Hy's Law Cases (Safety Analysis Set)
CT-10.5.1	Incidence of Laboratory Test Values With Potential Clinical Relevance - Prolactin (Safety Analysis Set)
CT-10.5.2	Listing of Laboratory Test Values With Potential Clinical Relevance - Prolactin (Safety Analysis Set)
CT-10.6.1	Incidence of Treatment-emergent Significant Change in Lipids (Safety Analysis Set)
CT-10.6.2	Listing of Treatment-emergent Significant Change in Lipids (Safety Analysis Set)

CT-10.7.1	Incidence of Treatment-emergent Significant Change in Glucose (Safety Analysis Set)
CT-10.7.2	Listing of Treatment-emergent Significant Change in Glucose (Safety Analysis Set)
CT-11.1	Mean Change From Baseline in Vital Signs (Safety Analysis Set)
CT-11.2	Incidence of Potentially Clinically Relevant Abnormalities in Vital Signs (Safety Analysis Set)
CT-11.3	Listing of Potentially Clinically Relevant Abnormalities in Vital Signs (Safety Analysis Set)
CT-11.4	Summary of Mean Change From Baseline by Study Week in Body Weight (kg) (Safety Analysis Set)
CT-11.5	Summary of Mean Change From Baseline by Study Week in BMI (kg/m^2) (Safety Analysis Set)
CT-11.6	Incidence of Potentially Clinically Relevant Weight Gain or Loss by Baseline BMI (Safety Analysis Set)
CT-12.1	Mean Change From Baseline in ECG Results (Safety Analysis Set)
CT-12.2	Shift Tables of ECG (Safety Analysis Set)
CT-12.3	Incidence of Categorical Increases in QT Evaluations (Safety Analysis Set)
CT-12.4	Incidence of Potentially Clinically Relevant Abnormalities in ECG Evaluations (Safety Analysis Set)
CT-12.5	Listing of Potentially Clinically Relevant Abnormalities in ECG Evaluations (Safety Analysis Set)
CT-13.1	Summary of Mean Change From Baseline by Study Week in DIEPSS (Safety Analysis Set)
CT-13.2	Summary of Mean Change From Baseline by Study Week in AIMS Total Score and Item Scores 8, 9 and 10 (Safety Analysis Set)
CT-13.3	Summary of Mean Change From Baseline by Study Week in BARS, Global Clinical Assessment of Akathisia (Safety Analysis Set)
CT-14.1	Summary of Mean Change From Baseline by Study Week in Sheehan-STS Score (Safety Analysis Set)
CT-14.2	Summary of Mean Change From Baseline by Study Week in Sheehan-STS - Total Score (Safety Analysis Set)
CT-14.3	Summary of Mean Change From Baseline by Study Week in Sheehan-STS - Suicidal Ideation Subscale Score (Safety Analysis Set)
CT-14.4	Summary of Mean Change From Baseline by Study Week in Sheehan-STS - Suicidal Behavior Subscale Score (Safety Analysis Set)
CT-15.1	Summary of Mean Change From Baseline by Study Week in ADCS-ADL Total Score (Safety Analysis Set)
CT-15.2	Summary of Mean Change From Baseline by Study Week in MMSE Total Score (Safety Analysis Set)

Appendix 5 List of Subject Data Listings

AE-1	Adverse Events (Subjects Assigned to Treatment)
DEMOG-1	Demographic Characteristics (Subjects Assigned to Treatment)
DREAS-1	Discontinued Subjects and Reason for Discontinuation (Subjects Assigned to Treatment)
LAB-1	Laboratory Test Results: Serum Chemistry (Subjects Assigned to Treatment)
LAB-2	Laboratory Test Results: Hematology (Subjects Assigned to Treatment)
LAB-3	Laboratory Test Results: Urinalysis (Subjects Assigned to Treatment)
LAB-4	Laboratory Test Results: Other Laboratory Tests (Subjects Assigned to Treatment)
LAB-5	Pregnancy Test (Subjects Assigned to Treatment)
EFF-1	Cohen-Mansfield Agitation Inventory (CMAI) (Subjects Assigned to Treatment)
EFF-2	Clinical Global Impression - Severity of Illness (CGI-S) (Subjects Assigned to Treatment)
EFF-3	Clinical Global Impression - Improvement (CGI-I) (Subjects Assigned to Treatment)
[redacted]	[redacted]
[redacted]	[redacted]
PDATA-1.1	Inclusion and Exclusion Criteria (Subjects Assigned to Treatment)
PDATA-1.2	Inclusion and Exclusion Criteria (Screening Failures)
PDATA-2	Treatment Assignment List (Subjects Assigned to Treatment)
PDATA-3	Study Completion Status and Reasons for Discontinuation (Subjects Assigned to Treatment)
PDATA-4	Medical History (Subjects Assigned to Treatment)
PDATA-5	Alzheimer's Disease History (Subjects Assigned to Treatment)
PDATA-6	Patient Care (Subjects Assigned to Treatment)
PDATA-7.1	Prior and Concomitant Medications (Subjects Assigned to Treatment)
PDATA-7.2	Prior and Concomitant Therapy (Subjects Assigned to Treatment)
PDATA-8	Physical Examination (Subjects Assigned to Treatment)
PDATA-9	Vital Signs (Subjects Assigned to Treatment)
PDATA-10	Electrocardiogram Results (Subjects Assigned to Treatment)
PDATA-11.1	Sheehan-Suicidality Tracking Scale (S-STS) - Other than Q15 and Q16 (Subjects Assigned to Treatment)
PDATA-11.2	Sheehan-Suicidality Tracking Scale (S-STS) - Q15 (Subjects Assigned to Treatment)
PDATA-11.3	Sheehan-Suicidality Tracking Scale (S-STS) - Q16 (Subjects Assigned to Treatment)
PDATA-12	Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) (Subjects Assigned to Treatment)
PDATA-13	Barnes Akathisia Rating Scale (BARS) (Subjects Assigned to Treatment)
PDATA-14	Abnormal Involuntary Movement Scale (AIMS) (Subjects Assigned to Treatment)
PDATA-15	Mini-Mental State Examination (MMSE) (Subjects Assigned to Treatment)
PDATA-16	Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) (Subjects Assigned to Treatment)
PDATA-17	Post-treatment Follow-up (Subjects Assigned to Treatment)
PDATA-18	Screening Failures
PDEV-1	Major Protocol Deviations by Type of Deviation (Subjects Assigned to Treatment)
SMED-1	Study Medication Administration (Subjects Assigned to Treatment)
SMED-2	Study Medication Compliance (Subjects Assigned to Treatment)
SUBEX-1	Subjects Excluded From Analysis Set (Subjects Assigned to Treatment)