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

ISN/Protocol 4345-CL-0015

ClinicalTrials.gov Identifier: NCT03557931

Date of Protocol: 17 Aug 2018

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

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Version 2.0

Incorporating Substantial Amendment 1 [See Attachment 1]

17 August 2018

IND 124721

Sponsor:

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

Protocol History:
Version 1.0 [06 Mar 2018]
Version 1.1 [08 Jun 2018]

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors and contributors, etc.) are located in [Section 14 Sponsor's Signatures].

2. INVESTIGATOR'S SIGNATURE

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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17 Aug 2018

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ----------

<Insert name and qualification of the Investigator>

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance** **Fax number: 1-888-396-3750** **Alternate Fax number: 1-847-317-1241** **Email: safety-us@astellas.com**
Medical Monitor/Study Physician:	PPD PPD, Medical Science Astellas Pharma Global Development PPD
Clinical Research Contacts:	PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF 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
anti-HAV	hepatitis A virus antibodies
anti-HCV	hepatitis C virus antibodies
APGD	Astellas Pharma Global Development, Inc.
ASSR	auditory steady-state response
AST	aspartate aminotransferase
ASST	attentional set-shifting task
AUC	area under the concentration-time curve
BARS	Barnes Akathisia Rating Scale
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
CA	Competent Authorities
CGI-S	Clinical Global Impression of Severity Scale
CI	confidence interval
CIAS	cognitive impairment associated with schizophrenia
CIOMS	council for international organizations of medical sciences
C_{max}	maximum concentration
CNS	central nervous system
COMT	catechol-O-methyltransferase
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP1A2	Cytochrome P450 1A2
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
D_1	dopamine receptor type 1
D_2	dopamine receptor type 2
D_3	dopamine receptor type 3
DILI	drug-induced liver injury
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
eCRF	electronic case report form
ED	extradimensional

Abbreviations	Description of abbreviations
EEA	European Economic Area
EEG	electroencephalography
EU	European Union
EoT	end-of-treatment
FAS	full analysis set
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transpeptidase
Glu	glutamate
GMP	good manufacturing practices
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
IB	investigator's brochure
ICD-10	International Statistical Classification of Diseases and Related Health Problem, 10th revision
ICF	informed consent form
ICH	international council for harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IgM	immunoglobulin M
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IRT	Interactive Response Technology
ISN	international study number
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
LA-CRF	liver abnormality case report form
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function tests
LS	least squares
MAD	multiple ascending dose
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MATRICS-CT	Measurement and Treatment Research to Improve Cognition in Schizophrenia Coprimary and Translations

Abbreviations	Description of abbreviations
MCCB	Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery
MedDRA	medical dictionary for regulatory activities
MDRD	Modification of Diet in Renal Disease
M.I.N.I. 7.02	M.I.N.I. International Neuropsychiatric Interview, version 7.02
MMRM	Mixed Models Repeated Measures
mPFC	medial prefrontal cortex
NIMH	National Institute of Mental Health
NOAEL	no-observed-adverse-effect-level
NSA-16	Negative Symptom Assessment Scale
NSAIDs	non-steroidal anti-inflammatory drugs
PAM	positive allosteric modulator
PANSS	Positive and Negative Symptom Scale
PCP	1-(1-phenylcyclohexyl) piperidine
PGx	pharmacogenetic
PKAS	pharmacokinetic analysis set
QD	daily
QTcF	QT interval using Fridericia's formula
SAD	single ascending dose
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SC	study coordinator
SCID-P	Structured Clinical Interview for DSM diagnoses
SE	standard error
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
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
VIM	Validation of Intermediate Measures

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
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.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	17 Aug 2018/Version 2.0
Sponsor: Astellas Pharma Global Development, Inc. (APGD)	**Protocol Number:** 4345-CL-0015
Name of Study Drug: ASP4345	**Phase of Development:** Phase 2a

Title of Study:
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

Planned Study Period:
From 3Q2018 to 1Q2020

Study Objective(s):
The objectives of the study, conducted in subjects with cognitive impairment associated with schizophrenia, are the following:

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

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

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 the 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

Planned Total Number of Study Centers and Location(s):
Up to approximately 25 centers in the United States

Study Population:

Male and female adult 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 and 2 months for depot medications.

Number of Subjects to be Enrolled/Randomized:

Approximately 420 subjects are planned to be screened for 210 subjects randomized to receive either 1 of 2 doses of ASP4345 or placebo in a 3:2:2 ratio (approximately 90 placebo subjects and 60 subjects each per active study arm).

Study Design Overview:

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)

Up to 210 subjects will be 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

After signing informed consent and during the screening period, study site personnel will check that potential subjects have not already been pre-screened, initiated or completed screening, or have been randomized into this study or another clinical trial using an independent subject participation database.

After completing the screening procedures, subjects will be evaluated for randomization eligibility. After randomization on day 1, subjects will receive oral doses of ASP4345 or matching placebo QD for 12 weeks. 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 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

Pharmacokinetic trough samples will be collected prior to dosing at days 7, 14 or 21, 42 and 84. Additional samples will be collected at approximately 2 hours and 4 hours post dose on day 42.

To determine changes in cognition with the MCCB instrument, cognitive testing will be performed at each screening visit, on days 1 (prior to first dose), 42 and 84. All MCCB assessments following randomization should be performed within a 2-hour window of the baseline test. In order to avoid an acute impact of nicotine and caffeine on cognitive testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCB assessment.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board/Independent Ethics Committee approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is a male or female subject between 18 to 55 years of age, inclusive, at screening.
3. Subject has a diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria and confirmed by the Mini-International Neuropsychiatric Interview version 7.02.
4. Subject has a stable clinical course as suggested by the following:
   - no psychiatric hospitalization within the last 4 months,
   - no symptom-related changes in psychotropic medications (as defined in the concomitant medication section) within 4 weeks prior to baseline for oral medications and within 2 months for depot medications,
   - and core positive symptoms no worse than moderate in severity and no evidence of a current severe major depressive episode (moderately severe depression is allowed).
5. Subject has a stable living situation.
6. Subject's extrapyramidal symptoms are no worse than mild in severity.
7. Subject must be in ongoing maintenance (i.e., at least 4 weeks prior to day 1 for oral medications and 2 months for depot medications) on up to 2 antipsychotic therapies (oral or depot) other than clozapine.
8. Subject has a body mass index range of 18.5 to 45.0 kg/m^2.
9. Female subject must either:
   - Be of nonchildbearing potential:
     - Postmenopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or
     - Documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
   - Or, if of childbearing potential,
     - Agrees not to try to become pregnant during the study and for 28 days after the final study drug administration,
     - And has a negative blood pregnancy test at screening and a negative urine pregnancy test at day 1,
     - And if heterosexually active, agrees to consistently use 1 form of highly effective birth control* starting at screening and throughout the study period and for 28 days after the final study drug administration.

10. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 28 days after the final study drug administration.
11. Female subject must not donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration.
12. A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
    - Agrees to use a male condom starting at screening and continue throughout study treatment and for 90 days after the final study drug administration.
13. Male subject must not donate sperm starting at screening and throughout the study period, and for 90 days after the final study drug administration.
14. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 90 days after the final study drug administration.
15. Subject agrees not to participate in another interventional study while participating in the present study, defined as signing the informed consent form until completion of the last study visit.
16. Subject has a negative urine drug screen for drugs of abuse at screening and day 1, excluding cannabis and documented prescribed benzodiazepines.

*Highly effective forms of birth control include:
- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine system (IUS).
- Bilateral tubal occlusion
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
- Male is sterile due to a bilateral orchiectomy
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion Criteria:

Subject will be excluded from participation if any of the following apply:

1. Subject has a known or suspected hypersensitivity to ASP4345 or any components of the formulation.
2. Subject has had previous exposure with ASP4345.
3. Subject has a history of suicide attempt or suicidal behavior within 1 year prior to screening or has any suicidal ideation that meets criteria at a level of 4 or 5 by using the Columbia Suicide Severity Rating Scale (C-SSRS) or who is at significant risk to commit suicide, as assessed by the investigator at screening or at day 1.
4. Subject has any clinically significant liver chemistry test result (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) or a result > 1.5 times above the upper limit of normal (ULN) at screening or repeated within 1 week prior to potential randomization (day 1). In such a case, the assessment may be repeated once.

5. Subject has any history or evidence of any clinically significant allergic, cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, history of seizure disorder, renal and/or other major disease or malignancy, as determined by the investigator.
6. Subject has any clinically significant abnormality following the investigator's review of the physical examination, electrocardiogram (ECG) and protocol-defined clinical laboratory tests at screening or at admission to the study (day 1).
7. Subject has known kidney disease and a glomerular filtration rate (GFR) < 60 mL/min per meter squared at screening and subjects will be discontinued from treatment only for decreases in the GFR that are clinically relevant.
8. Subject has a resting systolic blood pressure > 180 mmHg or < 90 mmHg, and a resting diastolic blood pressure > 100 mmHg at screening. These assessments may be repeated once, after a reasonable timeperiod, at the investigator's discretion (but within the screening period).
9. Subject has a mean corrected QT interval using Fridericia's formula (QTcF) > 450 msec (for male subjects) and > 470 msec (for female subjects) at screening or at randomization. If the mean QTcF exceeds the limits above, one additional triplicate ECG can be taken on day 1.
10. Subject has a history in the 6 months prior to screening of consuming more than 14 units of alcoholic beverages per week for males and more than 7 units of alcoholic beverages per week for females. (Note 1 unit = 12 ounces of beer, 4 ounces of wine, or 1 ounce of spirits).
11. Subject is currently using protocol-specified prohibited medications and is unable to washout, including over-the-counter products and agrees not to consume grapefruit and/or grapefruit juice (as defined in the concomitant medication section).
12. Subject is currently using clozapine for treatment of schizophrenia.
13. Subject has a positive test for hepatitis B surface antigen (HBsAg), hepatitis A virus antibodies (immunoglobulin M) (anti-HAV [IgM]) or hepatitis C virus antibodies (anti-HCV) at Screening or has history of a positive test for human immunodeficiency virus type 1(HIV-1) and/or type 2 (HIV-2).
14. Subject who has had electroconvulsive therapy within the 6 months prior to screening.
15. Subject has a history of head injury with clinically significant sequelae, including loss of consciousness for 1 hour or greater.
16. Subject is an employee of the Astellas Group or Contract Research Organization involved in the clinical study.
17. Subject has received investigational study drug within 28 days or 5 half-lives, whichever is longer, prior to screening.
18. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product(s):

ASP4345

Strengths: 50 mg capsules

Dose(s):

Dose range of 50 mg and 150 mg

Mode of Administration:

ASP4345 capsules will be administered orally as a single daily dose on days 2 through 84, in the morning with or without food (the first dose on day 1 will be taken at the study site). The subject will also dose at the study site on the following 4 visits: days 7, 14 **or** 21, 42 and 84/end-of-treatment (EoT).

Comparative Drug(s):

Placebo to match for ASP4345

Doses(s):

Not applicable

Mode of Administration:

Matching placebo capsules will be administered orally as a single daily dose on days 2 through 84, in the morning with or without food. Dosing at the study site will be performed at the designated timepoints noted above for the ASP4345 capsules.

Concomitant Medication Restrictions or Requirements:

Permitted Concomitant Antipsychotics:

Subjects are required to be on a stable dose of an antipsychotic or a stable regimen of up to 2 antipsychotics, for 4 weeks prior to baseline (i.e., day 1) for oral drugs and for 2 months prior to baseline for depot treatment and throughout the study. The subject will continue to take their prescribed antipsychotic throughout the study at their usual dosing time and interval. Permitted antipsychotics include quetiapine, risperidone, olanzapine, ziprasidone, aripiprazole, brexpiprazole, paliperidone or lurasidone.

Prohibited Concomitant Medications:

The following concomitant medications are prohibited:

- Use of clozapine for treatment of schizophrenia
- Initiation of medications during the conduct of the study that are inducers and inhibitors (strong and moderate) for enzymes cytochrome P450(CYP)2C19, CYP2D6 and CYP1A2 are prohibited to avoid potential confounding effects on the study results. See Appendix 12.2 List of Inducers and Inhibitors of CYP2C19, CYP2D6 and CYP1A2.
- Strong and moderate CYP3A inhibitor use (e.g., but not limited to: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole)
- Any nonprescribed drugs (including natural and herbal remedies [e.g., Valerian]) from 2 weeks prior to administration of the study drug

Allowed Concomitant Medications:

In addition to the antipsychotics listed above, the following concomitant medications at stable doses (i.e., 4 weeks prior to day 1) are allowed during the study:

- Stable doses of antidepressants (except for fluvoxamine, buproprion, tricyclic antidepressants, and monoamine oxidase inhibitors) are permitted
- Short-acting hypnotic agents (trazodone or zolpidem or zaleplon or zopiclone or eszopiclone (Note: Short-acting hypnotics are not allowed within 12 hours prior to cognitive testing)
- Anticholinergics are permitted (Note: use of anticholinergics is not allowed within 8 hours prior to cognitive testing)
- Approved use of concomitant medication for the treatment of hypertension, hyperlipidemia or diabetes mellitus
- Occasional use of non-steroidal anti-inflammatory drugs (NSAIDs) (including acetaminophen [up to 2 g/day], ibuprofen and naproxen)
- Vitamins and cardiovascular prophylactic aspirin up to 325 mg/day
- Any other prescribed medications are allowed during the study only after approval by the investigator in consultation with the study medical monitor

Duration of Treatment:

Once daily for 12 weeks (i.e., 84 days)

Formal Stopping Rules:

Individual Subject Stopping Criteria

Dosing of a subject will be discontinued in the event that any of the following criteria are fulfilled. The subject will be allowed to continue in the clinical 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.

If the following finding occurs in 2 consecutive measures within 24 hours study drug should be discontinued:

- ALT or AST ≥ 3 x ULN, or ALT or AST ≥ 2 x ULN and ALT or AST ≥ 5 x baseline value, or TBL ≥ 2 x ULN.

  These findings will be confirmed by repeat measurements within 48 hours. Generally liver enzymes will be followed by repeated measurements until they return to baseline or stable values.

If the following findings occur, the study drug should be immediately discontinued:

- QTcF ≥ 500 ms (confirmed on immediate repeat measurements).
- Serum creatinine increases > 26.52 µmol/L (0.3 mg/dL) in an absolute amount or increases > 1.5-fold greater than the baseline value or serum cystatin C > 2-fold greater than the baseline value for which there is no alternate clinical explanation.

Endpoints for Evaluation:

Primary Endpoints:

- 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 adverse events (AEs)
  - Vital signs (sitting or supine blood pressure, pulse and body temperature)
  - Clinical laboratory tests (hematology, biochemistry [including cystatin and serum prolactin] 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 [days 1 and 84/EoT] and fasting glucose), and hemoglobin A1c [HbA1c]
  - Movement disorder (Abnormal Involuntary Movement Scale [AIMS], Simpson Angus Scale [SAS] and Barnes Akathisia Rating Scale [BARS])

Secondary Endpoints:

- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the UPSA-2-ER instrument.
- Pharmacokinetics:
  - ASP4345 and its metabolites, if necessary (plasma) C_{trough} C_{maxss} and AUC_{ss} for ASP4345 and its metabolites, if necessary, will be estimated based on population pharmacokinetic modeling.

Exploratory 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 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 Clinical Global Impression of Severity Scale (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
- To evaluate the relationship between number of cognitive training levels achieved (as a measure of compliance with cognitive training) and MCCB
- 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

Statistical Methods:

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, 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 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.

Efficacy:

Analysis of the primary efficacy endpoint will be conducted on the full analysis set (FAS) and Intent-to-Treat (ITT) set. 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.

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

Based on the estimand, the primary endpoint will be analyzed using a Mixed Models Repeated Measures (MMRM) approach, with the corresponding score at baseline used as the covariate. Other continuous endpoints will be analyzed using either a MMRM or Analysis of Covariance (ANCOVA), depending on the schedule of events, with the corresponding scores at baseline used as a covariate. A 2-sided 90% confidence interval (CI) for the treatment difference in least squares (LS) mean changes between ASP4345 and placebo will be provided.

Sensitivity analyses of the primary efficacy endpoint and selected secondary/exploratory endpoints will be performed based on duration since the first psychotic break, smoking status, subject age, biotype and background antipsychotics.

Pharmacokinetics:

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.

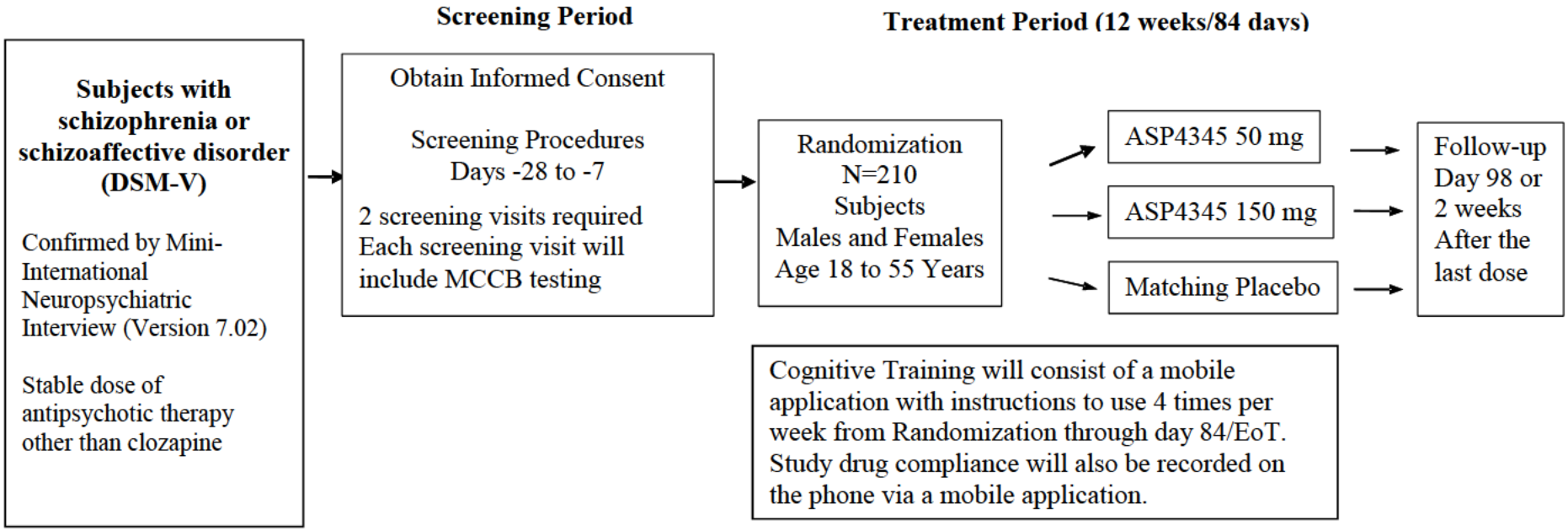
Pharmacogenetics:

The pharmacogenetic parameters, mentioned under exploratory endpoints, will be analyzed using either an MMRM or ANCOVA model, as used for the analysis of the primary and some of the secondary and exploratory efficacy endpoints.

Safety:

To characterize the safety profile, descriptive statistics will be provided for AEs, vital signs (body temperature, pulse rate and sitting or supine blood pressure), clinical laboratory evaluations (hematology and biochemistry [including serum prolactin]), routine 12-lead ECG recordings, C-SSRS, indices of metabolic syndrome, movement disorder, for each ASP4345 treatment and pooled placebo, where applicable.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS



DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EoT: End-of-treatment; MCCB: MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery

Table 1 Schedule of Assessments

Period	Screening		Treatment and Observation													Follow-up
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/ EoT	16
Visit Week	-4 to -3	-3 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	14
Visit Day	-28 to -21	-20 to -7	1	7	14	21	28	35	42	49	56	63	70	77	84	98/ EoS
Visit Window			-1 day (a)	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days (b)	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days (b)	±3 days
Informed Consent	X															
Verify Eligibility Criteria	X		X(a)													
Demographics, including Smoking History and use of Cannabis (c), Height, BMI	X															
Weight and Waist Circumference)	X		X(a)						X						X	
Medical and Psychiatric History	X		X(a)													
Duplicate Subject Database Check	X															
Mini-International Neuropsychiatric Interview	X															
Sponsor consult on concomitant medications)	X		X(a)													
Vital Signs (d)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12 Lead Electrocardiogram (e)	X		X						X						X	
Physical Examination	X		X						X						X	
Pregnancy Test (f, g)	X (f)		X (g)						X (g)						X (f)	X (f)
Urine Drug and Alcohol Test	X		X												X	
Hematology, Biochemistry,Urinalysis	X	X (h)						X (h)						X (h)		X
Abbreviated Biochemistry			X	X	X	X	X		X	X	X	X	X		X	
Serology for Hepatitis Testing	X															
Plasma Adrenocorticotropic Hormone and Prolactin			X												X	
MATRICS Consensus Cognitive Battery (i, j)	X	X	X (i)						X (i)						X (i)	
University of San Diego Performance-based Skills Assessment-2 Extended Range (a, b)			X												X	
Positive and Negative Syndrome Scale (a, b)	X		X(a)		X				X(b)						X (b)	
Negative Symptom Assessment-16 Scale (a, b)	X		X(a)						X(b)						X (b)	

Table continued on next page

Period	**Screening**		**Treatment and Observation**													**Follow-up**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/ EoT	16
Visit Week	-4 to -3	-3 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	14
Visit Day	-28 to -21	-20 to -7	1	7	14	21	28	35	42	49	56	63	70	77	84	98/ EoS
Visit Window			-1 day (a)	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days (b)	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days (b)	±3 days
Clinical Global Impression of Severity Scale	X	X	X(a)						X(b)						X (b)	
Randomization			X(a)													
Abnormal Involuntary Movement Scale			X(a)						X(b)						X (b)	
Simpson Angus Scale			X(a)						X(b)						X (b)	
Barnes Akathisia Rating Scale			X(a)						X(b)						X (b)	
Cognitive Training (a) and Study Drug Compliance via mobile applications (k)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Administration and Review (l)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Sampling for ASP4345 Pharmacokinetics (m, n)				X	X				X (n)						X	
Blood Sampling for Antipsychotic Pharmacokinetics			X						X						X	
Pharmacogenetic testing: COMT and dopamine D_1 and D_3 genotyping (o)			X													
Biobanking Sample for Retrospective PGx Analysis (o)			X													
Columbia-Suicide Severity Rating Scale (p)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking Status			X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: BMI: body mass index; C-SSRS: Columbia–Suicide Severity Rating Scale; COMT: catechol-O-methyltransferase; D_1: Dopamine Receptor Type 1; D_3: Dopamine Receptor Type 3; ECG: electrocardiogram; EoT: end-of- treatment; EoS: end-of-study; GFR: Glomerular Filtration Rate; ICF: informed consent form; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia; MCCB: Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery; NSA-16: Negative Symptom Assessment Scale; PANSS: Positive and Negative Symptom Scale; PGx: pharmacogenetic; QTcF: QT interval using Fridericia's formula; UPSA-2-ER: University of California San Diego Performance-based Skills Assessment-2 Extended Range

Footnotes continued on next page

(a) The following assessments can be performed on day -1: Verify Eligibilty Criteria (also day 1), Weight and Waist Circumference, Medical and Psychiatric History Review, sponsor consult on concomitant medications (if changes have occurred), Cognitive Training Mobile Application Set-up, Positive and Negative Syndrome Scale, Negative Symptom Assessment-16 scale, Clinical Global Impression of Severity Rating Scale, Abnormal Involuntary Movement Scale, Simpson Angus Scale, and Barnes Akathisia Rating Scale. ALL other assessments must be performed as listed on day 1.

(b) The following clinical assessments can be performed the day prior to days 42 and 84 visits: Positive and Negative Syndrome Scale, Negative Symptom Assessment-16 Scale, Clinical Global Impression of Severity Scale, Abnormal Involuntary Movement Scale, Simpson Angus Scale and Barnes Akathisia Rating Scale. Performing these assessments the day prior to days 42 and/or 84 is optional. All other assessments must be performed as listed on day 42 and day 84.

(c) Current and former history of smoking and use of cannabis (via smoking or ingestion) will be collected.

(d) Vital signs include body temperature, pulse and sitting or supine blood pressure.

(e) ECGs should be collected prior to pharmacokinetic sample collection at screening and days 1, 42 and 84/EoT. Prior to performing ECGs, subjects should rest in the supine position for at least 5 minutes. One additional triplicate ECG can be taken on day 1 if the QTcF exceeds the limits in Exclusion Criterion 9.

(f) Serum pregnancy tests will be performed for women of childbearing potential at the screening visit, and on days 84/EoT and 98/EoS.

(g) Urine pregnancy tests will be performed for women of childbearing potential only on days 1 and 42.

(h) Blood samples for glucose should be performed fasting at the second screening visit (baseline for this test), and days 35 and 77.

(i) All MCCB testing following randomization (i.e., days 42 and 84/EoT) should be performed within a 2 hour window of baseline (day 1).

(j) In order to avoid an acute impact of nicotine and caffeine on cognitive testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCB assessment.

(k) Cognitive Training will consist of a mobile application provided to the subject with instructions to use 4 times per week from randomization through day 84/EoT. The application will be reviewed with the subject at each visit to check compliance. Study drug compliance will also be recorded using a mobile application.

(l) Subjects will begin dose on day 1 of the study following all baseline procedures performed and randomization. At each subsequent weekly visit study drug will be counted for compliance and a new packet dispensed except for day 84/EoT.

(m) Pharmacokinetic trough samples will be collected prior to dosing at days 7, 14 **or** 21, 42 and 84/EoT.

(n) Additional pharmacokinetic samples will be collected at approximately 2 hours and 4 hours post dose on day 42.

(o) The samples for pharmacogenetic testing (COMT and dopamine D_1 and D_3 receptor genotyping) and biobanking for retrospective pharmacogenetic analysis are optional and will be collected at baseline (day 1) prior to dosing. ICFs for substudies may be collected prior to day 1 sample collection.

(p) The version of the C-SSRS to be performed at the first screening visit is the “Lifetime” version and the version of the C-SSRS to be performed on at the second screening visits and on days 1 though day 98/EoS is the “Since Last Visit.”

1 INTRODUCTION

Protocol 4345-CL-0015 is a proof-of-concept study to examine the effects of ASP4345 in subjects with cognitive impairment associated with schizophrenia on stable doses of risperidone, quetiapine, olanzapine, ziprasidone, aripiprazole, brexpiprazole, paliperidone or lurasidone.

1.1 Background

Schizophrenia is a chronically debilitating syndrome that affects approximately 1% of the global population and is accompanied by extraordinary high medical and economic burden [Awad & Voruganti, 2008]. The 3 primary clinical symptom domains of schizophrenia include positive symptoms (delusions and hallucinations), negative symptoms (apathy, blunted affect, anhedonia, avolition, alogia, social and emotional withdrawal) and a wide range of cognitive symptoms, in addition to a general disorganization of thinking and behavior [Tandon et al, 2009]. Cognitive impairment associated with schizophrenia (CIAS) includes significant deficits (approximately 1 standard deviation [SD] below performance of healthy control subjects) in attention/vigilance, processing speed, working memory, reasoning, problem solving, verbal memory, visual memory and social cognition that are present both in patients on antipsychotics, as well as drug-naïve patients [Fatouros-Bergman et al, 2014; Schaefer et al, 2013]. These impairments have been shown to be associated with several key functional outcomes [Shamsi et al, 2011; Green et al, 2000].

Dopamine is a neurotransmitter playing a key role in the central nervous system (CNS) [Snyder et al, 1970]. The physiological actions of dopamine are mediated by dopamine receptors, which belong to the G protein-coupled receptor superfamily. On the basis of their structural, pharmacological and biochemical properties, dopamine receptors are classified into either the D_1-class (dopamine receptor type 1 [D_1] and dopamine receptor type 5 receptors) or the D_2-class (dopamine receptor type 2, dopamine receptor type 3 and dopamine receptor type 4 receptors). Among them, D_1 receptors are expressed at a high level of density in the dopamine rich area of the forebrain and play a crucial role in a variety of cognitive functions [Zhang et al, 2009]. It is reported that abnormal neurotransmission, especially the dopamine and glutamate (Glu) system, plays a critical role in the pathophysiology of schizophrenia. One of the therapeutic targets for CIAS is the activation of D_1 receptors [Tamminga, 2006; Goldman-Rakic et al, 2004]. The hyperactivity of dopamine in subcortical structures is thought to be associated with positive symptoms; whereas, D_1 receptor hypoactivity in the frontal cortical area has been suggested to be associated with negative symptoms and impaired cognitive function [Laruelle, 2014]. Indeed, D_1 receptors in the frontal cortex are reported to be involved in working memory expression [Arnsten et al, 1994]. These findings indicate that the stimulation of the D_1 receptor is a promising target for improving CIAS; however, no D_1 receptor agonist has been identified as a drug candidate for CIAS because of their powerful hypotensive effect [Blanchet et al, 1998; Duncker et al, 1997].

Increased activation of D_1 receptors remains a compelling mechanism of action to treat CIAS, as identified by a consensus of academic and industry experts during the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative [Buchanan et al,

2007; Tamminga, 2006]. However, this mechanism has not been adequately tested in the clinic due to limitations of available D_1 receptor agonists. Positive allosteric modulators (PAMs) are an alternative option for stimulating receptor function. They positively modulate the effect of the agonist, which binds to the orthosteric site, without directly stimulating the receptor [May et al, 2004] and are therefore expected to exert agonist-like activity with a lower incidence of undesirable side effects. ASP4345 is an orally available, small-molecule and selective D_1 receptor PAM discovered by Astellas Pharma Inc. ASP4345 is expected to effectively ameliorate CIAS without side effects such as hypotension.

1.2 Nonclinical and Clinical Data

The PAM effect of ASP4345 on the human D_1 receptor was investigated using in vitro studies. In a cyclic adenosine monophosphate assay using human D_1 receptor-expressing cells, ASP4345 enhanced the potency of dopamine in a concentration-related manner. In a binding study, dopamine hydrochloride concentration-relatedly inhibited binding of [^{3}H]SCH23390, a D_1 receptor antagonist radioligand, to D_1 receptors. ASP4345 (10 μmol/L) positively modulated the dopamine -induced inhibitory activity. This result suggests that ASP4345 enhances the binding activity of orthosteric D_1 receptor ligands. ASP4345 at a concentration of 10 μmol/L had no appreciable affinity (less than 50% inhibition displacement of specific binding) to the D_1 receptor orthosteric site or 53 other receptors, ion channels and transporters.

At an in vivo level, the potentiating effect of ASP4345 on c-fos expression stimulated by a D_1 agonist at the medial prefrontal cortex (mPFC) was assessed in neonatally 1-(1-phenylcyclohexyl) piperidine (PCP)-treated mice. Oral treatment with 1 mg/kg ASP4345 enhanced the c-fos expression in (±)-SKF38393 hydrochloride (1 mg/kg)-treated mice.

It is widely accepted that cognitive deficits, including cognitive inflexibility are a core feature of schizophrenia. Cognitive flexibility may be assessed in rodents using the attentional set-shifting task (ASST). The effect on extradimensional (ED) shift deficits using the ASST was evaluated in subchronic PCP-treated rats. ASP4345 significantly ameliorated ED shift deficits at doses of 0.3 and 1 mg/kg.

The effect of ASP4345 on the release of neurotransmitters at the mPFC was assessed in subchronic PCP-treated rats using an in vivo microdialysis technique. Treatment of ASP4345 increased the γ-aminobutyric acid level at 1 and 30 mg/kg doses and dopamine efflux at the 1 mg/kg dose. Oral treatment of ASP4345 did not affect glutamate efflux at any dose.

In summary, results of both the in vitro and in vivo studies indicate that ASP4345 is an orally active D_1 receptor PAM and a promising candidate for use in treating CIAS.

The preclinical toxicology studies are reviewed in detail in the ASP4345 Investigator's Brochure. ASP4345 is considered a PAM with important findings noted below, including 1 rat death associated with renal toxicity at the highest dose in a toxicological study and while the reversibility of the renal toxicity was noted in survival animals. In dogs, vomiting, salivation, blood pH/electrolyte changes were observed but the histological changes in the kidney observed during the 1-week study were not replicated in the 4-week or 13-week

studies. Overall, the available toxicology data indicate that the target organs are the liver, kidneys, adrenal glands, ovary, gastrointestinal (vomiting and salivation) and possible embryo-fetal toxicity.

Safety, tolerability, and pharmacokinetics of ASP4345 have been evaluated in healthy male and female subjects in a single ascending oral dose escalation study (SAD; 4345-CL-0001) and further, in male and female subjects with schizophrenia in a multiple ascending oral dose escalation study (MAD; 4345-CL-0002) in phase 1. The mean exposure limit (AUC_{24} no greater than 14597 h•ng/mL) for the SAD and MAD studies were based on the no-observed-adverse-effect-levels (NOAELs) from the preclinical toxicology studies. A total of 92 subjects were treated with ASP4345 up to 900 mg single doses and 150 mg repeated doses during the phase 1 studies of 4345-CL-0001 and 4345-CL-0002.

ASP4345 was well-tolerated in the SAD study, consistent with the failure to identify a maximum tolerated dose and any clinically significant adverse reactions with single doses up to 900 mg (Study 4345-CL-0001). There were no deaths, serious adverse events (SAEs) or study discontinuations, and there were relatively few treatment-emergent or dose-related adverse events (AEs). Furthermore, there were not any apparent dose-related effect on the incidence of total or any specific AEs, laboratory results, electrocardiograms (ECGs) or vital signs.

ASP4345 was well-tolerated in the MAD study, also consistent with the failure to identify a maximum tolerated dose with multiple doses up to 150 mg/day over 14 days. In the MAD study (4345-CL-0002), mean steady-state conditions were reached by approximately day 5 of dosing across ASP4345 treatment groups, although 1 to 2 patients in each treatment group had more variability due to the length of time it took for these patients to reach steady-state. Mean steady-state AUC_{tau} did not exceed the mean exposure limit (AUC_{24}, day14 no greater than 14597 h•ng/mL) for any ASP4345 treatment group, including the 150 mg ASP4345 treatment group. However, median steady-state AUC_{tau} exceeded the exposure limit for the 150 mg treatment group.

The mean t½ ranged from 11.1 to 26.8 hours, with the highest mean value observed in the 50 mg ASP4345 treatment group. Rac (AUC) was similar across ASP4345 treatment groups and was approximately 1- to 2-fold at steady-state. There was no dose-dependency observed for rate of absorption (t_{max}), lag time (t_{lag}) or half-life ($t_{½}$). There was no evidence of time variant pharmacokinetics (e.g., auto-induction or -inhibition).

Based on the results of the slope estimates for the dose range tested (3 to 150 mg ASP4345), both C_{max} and AUC_{tau} failed to achieve dose proportionality at steady-state due to an unknown pharmacokinetic variable. The amount of ASP4345 excreted in urine was small with < 1% of the dose excreted unchanged.

Phamacodynamic effects of ASP4345 were also explored in the MAD trial by applying cognitive testing as well as EEG testing. The following tests were selected to cover a broad spectrum of cognitive domains thought to be modulated by dopamine to assess for any subtle changes in cognition as part of the specific CogState panel for schizophrenia: Detection

Tasks (psychomotor function and information processing), Identification Task (visual attention) and One Back Task (attention and working memory).

While the study was not powered to see significant differences (including the 90% confidence interval [CI]), the direction and magnitude of effect sizes for cognitive testing suggests that treatment with ASP4345 was associated with a benefit of psychomotor function, information processing and visual attention. For all doses of ASP4345, performance on the Detection Task was numerically superior to baseline and placebo on day 14 with effect sizes ranging from 0.577 to 0.993. Once treatment "stopped" these positive effects remained although they were reduced in magnitude. For all doses of ASP4345, performance on the Identification Task was numerically superior to placebo on day 14. There was no trend as compared to placebo for the One Back Task.

Neurophysiological EEG testing in this study included the Auditory Steady-state Response (ASSR), Mismatch Negativity (MMN) and P300 assessments (P3a-FZ, P3b-CZ, P3b-PZ) that were performed over a 2-hour period. Regarding the EEG results, ASSR showed a positive response as compared to placebo on day 14 for the 150 mg treatment group, while MMN shows trends for benefits over placebo across treatment groups, except the 50 mg ASP4345 treatment group.

There were no patient deaths, study drug-related SAEs or TEAEs leading to withdrawal of treatment. There was 1 SAE of small intestinal obstruction in a patient who received 50 mg ASP4345 on days 19 through 23 that was considered severe in nature. The last dose day for this patient was day 14, 5 days prior to the start of the SAE. The SAE was considered by the investigator to be not related to study drug and attributable to past medical history.

In multiple ascending dose study (4345-CL-0002), the more common TEAEs occurring in > 10% of patients in either the respective placebo group vs the ASP4345 group were headache (33.3%, 4/12 vs 25.0%, 9/36), somnolence (8.3%, 1/12 vs 19.4%, 7/36), dizziness (16.7%, 2/12 vs 5.6%, 2/36), insomnia (25.0%, 3/12 vs 8.3%, 3/36), back pain (none vs 11.1%, 4/36), abdominal pain (16.7%, 2/12 vs none) and constipation (none vs 13.9%, 5/36). Therefore, with respect to TEAEs there was no clear pattern of tolerability issues for ASP4345 compared with placebo in this study with a limited sample size and duration of treatment.

Given nonclinical evidence of potential renal toxicity, laboratory tests directly assessing renal function were evaluated. Cystatin C values were monitored for changes in kidney function throughout and after the end-of-treatment (EoT). In multiple ascending dose study (4345-CL-0002), no patients in any ASP4345 dose group had changes from baseline to day 14 in cystatin C values > 30% compared to baseline. There were no apparent dose-related effects on cystatin C values.

There were no clinically significant changes in hematology or other chemistry laboratory analytes. This included an absence of patients with a potentially clinically significant value for liver enzymes or total bilirubin. With respect to vital sign findings, there were no time- or dose-dependent changes apparent for pulse rates, systolic blood pressure or diastolic blood

pressure. The incidence of positive orthostatic challenge test results was low and there was no consistent pattern that would indicate a dose-related effect. There were also no study drug-related changes in weight, waist circumference or body mass index (BMI).

During study 4345-CL-0002, from a cardiac standpoint, no patient had a clinically significantly abnormal ECG result at baseline or any postbaseline time point through day 18 (96 hours after the last dose). No patient had a QT interval using Fridericia's formula (QTcF) value > 480 msec through day 14 or a > 30 msec change from baseline in QTcF.

No patient showed evidence of suicidal ideation based on C-SSRS results.

In summary, ASP4345 appeared safe and well-tolerated with respect to a 14-day treatment duration with daily doses up to 150 mg.

Please refer to the Investigator's Brochure for detailed information from nonclinical and clinical studies.

1.3 Summary of Key Safety Information for Study Drugs

Given the early stage of development, there are currently no expected AEs for ASP4345.

ASP4345 is considered a PAM with a relatively tolerable safety profile but with important preclinical toxicology findings noted below, including 1 rat death associated with renal toxcity at the highest dose in a toxicological study and while the reversibility of the renal toxicity was noted in survival animals. In dogs, vomiting, salivation, blood pH/electrolyte changes were observed but the histological changes in the kidney observed during the 1-week study were not replicated in the 4-week or 13-week studies. Overall, the available toxicology data indicate that the target organs are the liver, kidneys, adrenal glands, ovary, gastrointestinal (vomiting and salivation) and possible embryo-fetal toxicity.

ASP4345 may be associated with Treatment Emergent Adverse Events (TEAEs) based on the clinical studies. The following were key clinical observations: headache, somnolence, dizziness, insomnia, back pain, abdominal pain, and constipation.

A maximum tolerated dose was not identified in either the SAD study (4345-CL-0001) or the MAD study in subjects with schizophrenia (4345-CL-0002) using dosing up to 900 mg single doses and 150 mg daily doses that did not exceed the mean exposure limit (AUC_{24} no greater than 14597 h•ng/mL) that was based on the NOAEL from the preclinical toxicology studies.

Further information can be found in the Investigator's Brochure.

1.4 Risk Benefit Assessment

No clinical efficacy studies have been conducted to date with ASP4345 for the treatment of cognitive impairment associated with schizophrenia (CIAS). Therefore, the actual benefit of ASP4345 in the treatment of CIAS is unknown. There are no known risks unambiguously identified with this mechanism of action, as ASP4345 is a first-in-class compound for the proposed indication. Based on the safety profile from the phase 1 clinical studies and especially with subjects with schizophrenia, proceeding to phase 2 trials appear to be justified from a risk benefit assessment.

An overview of the risk benefit of ASP4345 can be found in the Investigator's Brochure, including monitoring and mitigation steps taken to maintain safety of the subjects while on study treatment. Routine risk minimization procedures are planned in this study along with weekly visits, including laboratory assessments, so that increases in cystatin C suggesting renal toxicity can be detected if a longer duration of treatment is related to the risks. Due to the known effects of the antipsychotic therapies used in this study and a potential interaction with ASP4345, prolactin will also be monitored. Other risks are monitorable and reversible (liver toxicity by LFTs; adrenal gland vacuolation by adrenocorticotropic hormone). Additional potential risks are reversible (vomiting and salivation), therefore, no additional safety monitoring is required. Other potential risks such as changes in blood pH/blood chloride were likely due to the salt load for the administered dose and are unlikely to be of relevance for human studies associated with lower drug exposures. Changes in blood pH/blood chloride were not observed during phase 1 studies. Therefore, only chloride will be monitored in this study but for general monitoring of renal function as described above.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

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 and Dose Rationale

2.2.1 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

After signing informed consent and during the screening period, study site personnel will check that potential subjects have not already been pre-screened, initiated or completed screening or have been randomized into this study, or another clinical trial, using an independent subject participation database.

After completing the screening procedures, subjects will be evaluated for randomization eligibility. After randomization on day 1, subjects will receive oral doses of ASP4345 or matching placebo QD for 12 weeks. 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.

Pharmacokinetic trough samples will be collected prior to dosing at days 7, 14 or 21, 42 and 84. Additional samples will be collected at approximately 2 hours and 4 hours post dose on day 42.

To determine changes in cognition with the MCCB instrument, cognitive testing will be performed at each screening visit, on days 1 (prior to first dose), 42, and 84. All MCCB assessments following randomization should be performed within a 2-hour window of the baseline test. In order to avoid an acute impact of nicotine and caffeine on cognitive testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCB assessment.

Study day 84/EoT visit completes the treatment period for the subject. Subjects will return to the clinic for a follow-up visit on day 98 to complete the final assessments. Individual subject discontinuation of study drug treatment or study is addressed in Section 6 Discontinuation. Once the subject has completed or discontinued the study, no further treatment with ASP4345 for cognitive impairment is planned to be offered.

2.2.2 Dose Rationale

Astellas is proposing to conduct this PoC trial with separate 50 and 150 mg ASP4345 dose groups. This decision is based on the pharmacokinetic data and positive results for the *a priori* chosen electroencephalogram (EEG) evoked response and improvements in cognition (based on a specific CogState panel for schizophrenia) that were obtained for the ASP4345 50 and 150 mg dose groups as compared with placebo in 4345-CL-0002. An additional reason is not having observed safety or adverse events of concern in the of the multiple ascending oral dose study (4345-CL-0002). Further reasoning behind these dose choices follows.

ASP4345 is a D_1 receptor PAM and it is standard to evaluate 2 doses for a PAM or agonist, especially for a target where there is nonclinical data for both nonhuman primates and rodents suggesting potential inverted U dose (exposure)-response relationships. Both doses are within the presumptive nonclinical efficacious exposure range and evidence has been observed for

doses ranging from 3 to 150 mg. The 50 mg dose is the next highest dose to the 150 mg dose and data from the 50 mg dose will be valuable if safety data with the 150 mg dose are found to be inadequate.

Since the mean half-life of ASP4345 is approximately 10 to 20 h and patients achieved steady-state in the ongoing study by day 14, the pharmacokinetic parameters in a 12-week study are expected to be similar to the pharmacokinetic parameters observed on day 14 in Study 4345-CL-0002.

The ability of ASP4345 to improve cognitive impairment in subjects with schizophrenia will be assessed at doses of 50 mg and 150 mg QD over a period of 12 weeks.

2.3 Endpoints

2.3.1 Primary Endpoints

- 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, 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])

2.3.2 Secondary Endpoints

- Change from baseline to week 12/EoT for ASP4345 compared to placebo for the UPSA-2-ER instrument
- Pharmacokinetics:
  - ASP4345 and its metabolites, if necessary (plasma) $C_{trough.}$ C_{maxss} and AUC_{ss} for ASP4345 and its metabolites, if necessary, will be estimated based on population pharmacokinetic modeling

2.3.3 Exploratory 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 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

3 STUDY POPULATION

3.1 Selection of Study Population

Male and female adult 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 and 2 months for depot medications.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board/Independent Ethics Committee approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is a male or female subject between 18 to 55 years of age, inclusive, at screening.
3. Subject has a diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria and confirmed by the Mini-International Neuropsychiatric Interview version 7.02.
4. Subject has a stable clinical course as suggested by the following:
    - no psychiatric hospitalization within the last 4 months,
    - no symptom-related changes in psychotropic medications (as defined in the concomitant medication section) within 4 weeks prior to baseline for oral medications and within 2 months for depot medications,
    - and core positive symptoms no worse than moderate in severity and no evidence of a current severe major depressive episode (moderately severe depression is allowed).
5. Subject has a stable living situation.
6. Subject's extrapyramidal symptoms are no worse than mild in severity.

7. Subject must be in ongoing maintenance (i.e., at least 4 weeks prior to day 1 for oral medications and within 2 months for depot medications) on up to 2 antipsychotic therapies (oral or depot) other than clozapine.
8. Subject has a body mass index range of 18.5 to 45.0 kg/m^2.
9. Female subject must either:
    - Be of nonchildbearing potential:
        - Postmenopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or
        - Documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
    - Or, if of childbearing potential,
        - Agrees not to try to become pregnant during the study and for 28 days after the final study drug administration,
        - And has a negative blood pregnancy test at screening and a negative urine pregnancy test at day 1,
        - And if heterosexually active, agrees to consistently use 1 form of highly effective birth control* starting at screening and throughout the study period and for 28 days after the final study drug administration.
10. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 28 days after the final study drug administration.
11. Female subject must not donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration.
12. A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
    - Agrees to use a male condom starting at screening and continue throughout study treatment and for 90 days after the final study drug administration.
13. Male subject must not donate sperm starting at screening and throughout the study period, and for 90 days after the final study drug administration.
14. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 90 days after the final study drug administration.
15. Subject agrees not to participate in another interventional study while participating in the present study, defined as signing the informed consent form until completion of the last study visit.
16. Subject has a negative urine drug screen for drugs of abuse at screening and day 1, excluding cannabis and documented prescribed benzodiazepines.

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine system (IUS).
- Bilateral tubal occlusion
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
- Male is sterile due to a bilateral orchiectomy
- Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has a known or suspected hypersensitivity to ASP4345 or any components of the formulation.

2. Subject has had previous exposure with ASP4345.

3. Subject has a history of suicide attempt or suicidal behavior within 1 year prior to screening or has any suicidal ideation that meets criteria at a level of 4 or 5 by using the Columbia Suicide Severity Rating Scale (C-SSRS) or who is at significant risk to commit suicide, as assessed by the investigator at screening or at day 1.

4. Subject has any clinically significant liver chemistry test result (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) or a result > 1.5 times above the upper limit of normal (ULN) at screening or repeated within 1 week prior to potential randomization (day 1). In such a case, the assessment may be repeated once.

5. Subject has any history or evidence of any clinically significant allergic, cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, history of seizure disorder, renal and/or other major disease or malignancy, as determined by the investigator.

6. Subject has any clinically significant abnormality following the investigator's review of the physical examination, electrocardiogram (ECG) and protocol-defined clinical laboratory tests at screening or at admission to the study (day 1).

7. Subject has known kidney disease and a glomerular filtration rate (GFR) < 60 mL/min per meter squared at screening and subjects will be discontinued from treatment only for decreases in the GFR that are clinically relevant.

8. Subject has a resting systolic blood pressure > 180 mmHg or < 90 mmHg, and a resting diastolic blood pressure > 100 mmHg at screening. These assessments may be repeated once, after a reasonable time period, at the investigator's discretion (but within the screening period).
9. Subject has a mean corrected QTcF > 450 msec (for male subjects) and > 470 msec (for female subjects) at screening or at randomization. If the mean QTcF exceeds the limits above, one additional triplicate ECG can be taken on day 1.
10. Subject has a history in the 6 months prior to screening of consuming more than 14 units of alcoholic beverages per week for males and more than 7 units of alcoholic beverages per week for females. (Note 1 unit = 12 ounces of beer, 4 ounces of wine, or 1 ounce of spirits).
11. Subject is currently using protocol-specified prohibited medications and is unable to washout, including over-the-counter products and agrees not to consume grapefruit and/or grapefruit juice (as defined in the concomitant medication section).
12. Subject is currently using clozapine for treatment of schizophrenia.
13. Subject has a positive test for hepatitis B surface antigen (HBsAg), hepatitis A virus antibodies (immunoglobulin M) (anti-HAV [IgM]) or hepatitis C virus antibodies (anti-HCV) at Screening or has history of a positive test for human immunodeficiency virus type 1(HIV-1) and/or type 2 (HIV-2).
14. Subject who has had electroconvulsive therapy within the 6 months prior to screening.
15. Subject has a history of head injury with clinically significant sequelae, including loss of consciousness for 1 hour or greater.
16. Subject is an employee of the Astellas Group or Contract Research Organization involved in the clinical study.
17. Subject has received investigational study drug within 28 days or 5 half-lives, whichever is longer, prior to screening.
18. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug

ASP4345 will be supplied as 50 mg capsules for oral administration in hard gelatin capsules with a yellow cap and Swedish orange body.

The capsules are packaged in aluminum/aluminum blister strips, which are contained in a tri-fold dosing card. ASP4345 capsules are stored at ambient room temperature 20° - 25° C (68° - 77° F). Excursions are permitted between 15° and 30° C (59°and 86° F).

ASP4345 capsules are released in accordance with Good Manufacturing Practice (GMP) by Astellas.

4.1.2 Comparative Drug

Matching placebo will be supplied in the same packaging configuration as ASP4345 and has the same storage requirements.

4.2 Packaging and Labeling

All study drug(s) used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD or sponsor's designee in accordance with APGD or sponsor's designee Standard Operating Procedures (SOPs), GMP guidelines, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each dosing card will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator/or designee and that:

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Only study drug with appropriate expiry/retest is dispensed to study subjects in accordance with the protocol, and
- Any unused study drug is returned to the sponsor.

Study drug inventory and accountability records will be kept by the investigator or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator or designee (i.e., study drug manager) agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.

- The investigator or designee (i.e., study drug manager) will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator or designee (i.e., study drug manager). The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee (i.e., study drug manager) agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site staff must return study drug to the sponsor or designee at the end of the study or upon expiration unless otherwise approved by the sponsor.

4.4 Blinding

This is a double blind study. Subjects will be randomized to receive ASP4345 or placebo in a blinded fashion such that the investigator, sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

4.4.1 Blinding Method

This is a double blind study. Subjects will be randomized to receive 1 of 2 doses of ASP4345 or placebo in a blinded fashion such that neither the investigator, Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the IRT.

The randomization list will be provided to Global Pharmacovigilance of Astellas, who will break the codes for all Suspected Unexpected Serious Adverse Reaction (SUSAR) cases for reporting purposes only. They are also capable of breaking the code in emergency situations. The randomization list is also provided to BioAnalysis Scientist for the purposes of pharmacokinetic analysis prior to unblinding. The pharmacokinetic analysis results will not be shared prior to unblinding at database lock.

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

The appearance and the form of both the drug and packaging of the ASP4345 50 mg capsules are identical to those of the matching placebo.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study medication blind will be maintained by the IRT system.

4.4.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. The treatment code must only be requested by the investigator or other persons designated as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study drug should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study drug was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study drug.

4.4.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience a SUSAR, in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

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. Specific procedures for randomization through the IRT are contained in the study procedures manual.

If a subject is assigned a randomization number, but does not receive study drug, the randomization number will not be used again. The randomization schedules that determine subject treatment will be computer-generated by IRT before the beginning of the study. Specific procedures for randomization through the IRT are contained in the study-specific IRT manual.

All subject numbers will be assigned using the IRT starting at screening. All subjects will have a unique, 10-digit subject number. The first 5 digits of this number will be the investigator's site number. The second 5 digits will be represent the subject's accession number. This will be the number that identifies a subject during the course of the study.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

Subjects randomized to either of the ASP4345 groups will receive ASP4345 50 mg (1 capsule of 50 mg and 2 capsules of placebo) or ASP4345 150 mg (3 capsules of 50 mg and no placebo) QD for the duration of 12 weeks. Subjects randomized to the placebo group will receive placebo to match ASP4345 (3 capsules) QD for the duration of 12 weeks.

ASP4345 capsules will be administered orally as a single daily dose on days 2 through 84, in the morning with or without food (the first dose on day 1 will be taken at the study site). The subject will also dose at the study site on the following 4 visits: days 7, 14 **or** 21, 42 and 84/EoT.

Doses should be taken in the morning with or without food. If a subject forgets a dose, the dose should be taken as soon as they remember but prior to bedtime that day. The next day's dose should still be taken as planned. Two doses should not be taken in the same day.

At randomization and weekly thereafter, subjects will receive the assigned treatment sufficient for a period of 1 week with a 2-day window (including morning dose on the day of the next visit).

Pharmacokinetic samples will be taken pre-dose on day 7, 14 or 21, 42 and 84; post-dose at approximately 2 and 4 hours on day 42 (Week 6). There are no fasting requirements for the pharmacokinetic samples but date and time of the dose taken prior to collecting the pharmacokinetic sample will be captured in the electronic case report form (eCRF).

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

The doses of 50 and 150 mg QD of ASP4345 were tested in the phase 1 multiple dose study. These doses were well tolerated and no maximum tolerated dose was determined. Stopping criteria are presented in Section 6.1 Discontinuation of Individual Subject(s). Study 4345-CL-0015 is a fixed dose, proof-of-concept study. In order to adequately evaluate the hypothesis, it is important to assess efficacy and safety across a common dose, therefore, dose increases and decreases are not allowed.

5.1.3 Previous and Concomitant Treatment (Medication and NonMedication Therapy)

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 documented in the appropriate case report form as prior schizophrenia medications or other prior medication, respectively. Subjects taking prohibited medications who are willing to discontinue these medications, as clinically indicated and based upon the investigator's recommendation, may washout over a period of 5 half-lives on a schedule determined by the investigator in consultation with the study medical monitor.

Medications taken after the first dose of study medication and up to EoS will be documented on the appropriate case report form as concomitant medication.

During screening and prior to randomization, the investigator or designee will submit the subject's list of medications to the study medical monitor for review and approval. Subjects are instructed not to take any concomitant medication without first consulting the Investigator or study coordinator (SC) throughout the duration of the study.

Permitted Concomitant Antipsychotics:

Subjects are required to be on a stable dose of an antipsychotic, or a stable regimen of up to 2 antipsychotics, for 4 weeks prior to baseline (i.e., day 1) for oral drugs and for 2 months prior to baseline for depot treatment and throughout the study. The subject will continue to take their prescribed antipsychotic throughout the study at their usual dosing time and interval. Permitted antipsychotics include quetiapine, risperidone, olanzapine, ziprasidone, aripiprazole, brexpiprazole, paliperidone or lurasidone.

Prohibited Concomitant Medications:

The following concomitant medications are prohibited:

- Use of clozapine for treatment of schizophrenia.
- Strong and moderate CYP3A inhibitor use (e.g., but not limited to: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole).
- Initiation of medications during the conduct of the study that are inducers and inhibitors (strong and moderate) for enzymes cytochrome P450(CYP)2C19, CYP2D6 and CYP1A2 are prohibited to avoid potential confounding effects on the study results. See Appendix 12.2 List of Inducers and Inhibitors of CYP2C19, CYP2D6 and CYP1A2.
- Any nonprescribed drugs (including natural and herbal remedies [e.g., Valerian]) from 2 weeks prior to administration of the study drug.
- For a list of prohibited concomitant medications see Appendix 12.1 List of Excluded Concomitant Medications.

Allowed Concomitant Medications:

In addition to the antipsychotics listed above, the following concomitant medications at stable doses (i.e., 4 weeks prior to day 1) are allowed during the study:

- Stable doses of antidepressants (except for fluvoxamine, buproprion, tricyclic antidepressants, and monoamine oxidase inhibitors) are permitted
- Short-acting hypnotic agents (trazodone or zolpidem or zaleplon or zopiclone or eszopiclone (Note: Short-acting hypnotics are not allowed within 12 hours prior to cognitive testing)
- Anticholinergics are permitted (Note: use of anticholinergics is not allowed within 8 hours prior to cognitive testing)

- Approved use of concomitant medication for the treatment of hypertension, hyperlipidemia or diabetes mellitus
- Occasional use of non-steroidal anti-inflammatory drugs (NSAIDs) (including acetaminophen [up to 2 g/day], ibuprofen and naproxen)
- Vitamins and cardiovascular prophylactic aspirin up to 325 mg/day
- Oral contraceptive use is permitted as long as the subject is on a stable dose prior to screening.
- Any other prescribed medications are allowed during the study only after approval by the investigator in consultation with the study medical monitor.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each monthly visit after day 1. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Additionally, study drug compliance will also be documented by the use of a clinically-validated artificial intelligence technology application.

Subjects who are less than 85% compliant and more than 100% compliant with the dosage regimen for greater than 2 consecutive visit periods during the study should be counseled regarding steps to improve compliance. Subject use of the cognitive training application should also be assessed as outlined in Section 5.7.5 at the same time as compliance with study drug treatment.

Treatment compliance should be monitored closely and deviation in compliance should be reported to the sponsor.

5.1.5 Restrictions During the Study

Subjects are requested not to eat grapefruit and/or drink grapefruit juice (see exclusion criterion 11). Subject smoking is not restricted.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics including Smoking History

Date of birth, sex, race, ethnicity, height, weight, and BMI will be recorded at screening. Height will be measured at screening only. Weight and waist circumference will also be collected prior to randomization and on days 1, 42 and 84 as part of the assessment for metabolic syndrome described in Section 5.4.6 Metabolic Parameters.

Smoking history will be recorded at screening, including use of cannabis.

5.2.2 Medical and Psychiatric History

A detailed medical history for each subject will be obtained at screening, including a history of prior head trauma and treatment. A detailed psychiatric history will also be obtained at screening, including all treatments and therapies used. All relevant past and present conditions, as well as prior surgical procedures will be recorded.

5.2.3 Duplicate Subject Database Check

After signing informed consent and during the screening period, study site personnel will check that potential subjects have not already been pre-screened, initiated or completed screening, or have been randomized into this study or another clinical trial using an independent subject participation database. Independent subject participation databases seek to reduce duplicate enrollment by identifying duplicates before they randomize into the study, and this measure is consistent with exclusion requirement of not participating in another interventional clinical trial during the conduct of the study (inclusion criterion 15). In order to complete this check and per the informed consent, study personnel will request that the subject present a valid picture identification (e.g., driver's license, passport, state issued ID card, etc.) and study personnel may be required to provide certain authorized information that could potentially be used to identify study subjects identifiers (e.g., date of birth, initials, etc.) so that the match algorithms can be run.

Subjects that meet the inclusion criteria, none of the exclusion criteria, and are not identified as a duplicate subject (e.g., certainly, possible, probably), will be enrolled into the study. Appropriate documentation reflecting the subject's eligibility according to these criteria will be reflective in the subject's source documents.

5.2.4 Diagnosis of the Target Disease, Severity, and Duration of Disease

The diagnosis of schizophrenia or schizoaffective disorder must be confirmed by the investigator and documented in the subject's medical notes as meeting the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria and the criteria from the Mini-International Neuropsychiatric Interview version 7.02 at screening. Duration of schizophrenia or schizoaffective disorder, date of the first psychotic break and associated symptoms (agitation, delusions, hallucinations, and thought disorder) and date of the most recent psychotic break and associated symptoms (agitation, delusions, hallucinations, and thought disorder) will be recorded in the eCRF.

The subject's medical notes at screening must also confirm no psychiatric hospitalization within the last 4 months, no symptom-related changes in psychotropic medications (as defined in the concomitant medications section), core positive symptoms no worse than moderate in severity, and no evidence of a current severe major depressive episode. The subject must also have a stable living situation documented in the medical notes at screening.

5.2.5 Mini-International Neuropsychiatric Interview

The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I. 7.02) is a short, structured diagnostic interview administered by trained personnel. The instrument captures the major Axis I psychiatric disorders in Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) and ICD-10, and has demonstrated equivalent reliability, validity, and decreased interview time when compared to the Structured Clinical Interview for DSM-V diagnoses (SCID-P). Each module begins with screening questions that are answered yes or no. A negative response in the screening algorithm advances the interview to the next module, whereas a positive response will prompt additional questions that ask patients to characterize behavior with "yes" or "no" responses. Some questions contain a recall period (e.g., "Past Two Weeks," "Past Episode" and "Current Episode"). After completion of the additional questions, the clinician indicates whether or not the diagnostic criteria have been met, based on the instrument scoring criteria [Amorim et al, 1998; Sheehan et al, 1998; Lecrubier et al, 1997; Sheehan et al, 1997].

The M.I.N.I. 7.02 will be completed at screening on paper by trained site personnel, in accordance with the structured interview requirements.

5.3 Efficacy and Pharmacokinetics Assessments

5.3.1 Efficacy Assessments

The principal investigator or qualified delegate will complete the MCCB and UPSA-2-ER using a paper copy of the licensed instrument and the results will be recorded in a central database by the vendor following scoring of the scales. The data will be transferred electronically to the Sponsor.

For the NSA-16, PANSS, and CGI-S a tablet will be used by the principal investigator or qualified delegate to assess the subject during clinic visits. Site personnel will receive training on how to complete the assessments on the tablet. Data will be automatically transmitted to a central database from the tablet.

When possible continuity of raters should be maintained across scales for each patient. See [Appendix 12.6 Clinical Outcome Assessment Scales] for information on all COAs used in the study.

5.3.1.1 MATRICS Consensus Cognitive Battery

The MCCB was developed as a standard battery for clinical trials of cognition-enhancing interventions for schizophrenia. The instrument measures seven separate but intercorrelated cognitive domains: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning/problem solving, speed of processing and social cognition. These domains were the consensus of the National Institute of Mental Health (NIMH) *Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) initiative. The output of this process (test-retest reliability, utility as a repeated measure, relationship to functional outcome, potential sensitivity to pharmacological treatment and

practicality/tolerability from 5 clinical sites) was published as the 7-domain MCCB [Nuechterlein et al, 2008].

The MCCB should be completed by the principal investigator or qualified delegate twice during the 28-day screening period, and on days 1, 42 and 84/EoT. The data will be completed on paper by the principal investigator or qualified delegate.

5.3.1.2 University of San Diego Performance-based Skills Assessment-2 Extended Range

The UPSA-2 was developed to assess the functional abilities of the subject with schizophrenia in 6 domains: household management, communication, financial skills, transportation, comprehension/planning and medication management. The assessment is performed as a role-play with the rater in which participants are asked to utilize props to demonstrate how well they perform every day activities. The UPSA-2-ER contains additional questions to increase the level of difficulty for each subscale.

As part of the MATRICS Coprimary and Translations (MATRICS-CT) initiative, the Validation of Intermediate Measures (VIM) study established that the UPSA-2 demonstrated good test-retest reliability, was not burdensome to patients and was adequate for repeated measurements. The VIM study also demonstrated that performance-based measures were strongly correlated to cognition interview-based measures. Based on the available evidence, the MATRICS-CT initiative concluded that the UPSA-2 was suitable as a coprimary measure [Green et al, 2011]. Additional evidence has demonstrated correlation with the MCCB battery [Keefe et al, 2011]. In a study reported by Patterson and colleagues [2001], the UPSA-2 performance correlated significantly with the severity of negative symptoms and symptoms of cognitive impairment. As described above, the UPSA-2-ER contains additional questions to increase the level of difficulty for each subscale and has been used in previous CIAS trials.

The UPSA-2-ER scoring will be completed by the principal investigator or qualified delegate on paper on days 1 and 84/EoT.

5.3.1.3 Positive and Negative Syndrome Scale

The PANSS was developed based on patient interviews [Kay et al, 1987] and has been widely used in schizophrenia trials. The validity and reliability of the PANSS has been extensively studied and established [Lindenmayer et al, 1995], including its ability to assess positive and negative symptoms in subjects with recent onset of schizophrenia [Emsley et al, 2003]. The PANSS contains 30-items rated on 7-point Likert scales and is scored to assess 3 subscales: positive symptoms, negative symptoms and psychopathological symptoms. A 5-factor structure has also been identified to explore changes in the traditional subscales, and also those that may align with disorganized (or cognitive) factors, as well as excited and depression/anxiety factors [Lindenmayer et al, 1995].

Data from the PANSS is enhanced when subjects identify a person who can serve as an informant for its completion. Although not required for inclusion, sites and subjects are highly encouraged to identify a reliable subject (e.g., family member, social worker or case manager) who spends sufficient time with them to be able to provide information to PANSS raters and who has interacted with the subject during the past seven days.

The informant needs to be able and willing to attend clinic visits or to provide input via telephone. The same informant should be used throughout the study whenever possible. The informant must be considered to be reliable by the site.

The PANSS will be completed by the principal investigator or qualified delegate on the tablet at screening and days 1, 14, 42 and 84/EoT.

5.3.1.4 Negative Symptom Assessment-16

The NSA-16 [Axelrod et al, 1993] is a semi-structured interview conducted by the principal investigator or qualified delegate to determine the severity of the subject's negative symptoms in the areas of problems in communication, emotion and/or affect, motivation, and sociality. Based on a 7-point scale (0-6) for each of the 16 items, a total negative symptom score is calculated by adding the items; a higher score indicates more severe symptoms. The negative symptom burden will be further assessed using NSA-16 for patients who have at least 1 negative symptom of moderate severity. While some overlap between concepts on the PANSS negative symptom subscale and the NSA-16 exist, the NSA-16 assesses additional concepts covering verbal skills and activities of daily living, both of which may change if improved cognition is observed.

The NSA-16 will be completed by the principal investigator or qualified delegate on the tablet at screening and days 1, 42 and 84/EoT.

5.3.1.5 Clinical Global Impression of Severity Scale

The CGI-S [Schneider et al., 1997] is used to measure severity, treatment response and the efficacy of treatment in studies of patients with mental disorders. The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patients illness.

The CGI-S will be completed by the principal investigator or qualified delegate on the tablet at days 1, 42 and 84/EoT.

5.3.2 Pharmacokinetics Assessments

Pharmacokinetic trough samples will be collected at/on 4 visits: prior to dosing at days 7, 14 or 21, 42 and 84. Additional samples will be collected at approximately 2 hours and 4 hours post dose on day 42. Subjects should be reminded not to dose at home prior to their clinic visit.

Details on sample collection, processing, labeling, storage, and shipment procedures are provided in the laboratory manual. Analysis of ASP4345 and any metabolites (if applicable) will be performed using a validated method at a bioanalytical laboratory specified by the Sponsor.

5.4 Safety Assessment

Safety will be assessed through AEs, safety laboratory tests (chemistry, hematology and urinalysis), physical examination, vital signs, 12-lead ECGs, metabolic syndrome assessment (weight, waist circumference, cholesterol, triglycerides, HDL [the second screening visit and day 77] and fasting glucose), HbA1c and the C-SSRS. Unscheduled assessments will be performed if clinically warranted. The ARCI and Bond Lader instruments did not reveal any effects of ASP4345 during phase 1. Therefore, they are not included in the safety assessments. Phase 1 testing with ASP4345 has not revealed a clinically significant effect with orthostatic vital signs and these measures are not included in this trial.

ASP4345 penetrates the CNS in humans; therefore, a prospective assessment of suicidality will be performed using the C-SSRS.

5.4.1 Vital Signs

Vital signs consist of body temperature, pulse and sitting or supine blood pressure. Single measures of vital signs will be obtained during the screening visit, and at each weekly visit through day 84/EoT. Vital signs should be obtained prior to scheduled blood draws.

5.4.2 Adverse Events

See [Section 5.5 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.3 Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in Liver Function Tests value ([LFT], e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. See Table 1 Schedule of Assessments for study visit collection dates.

Panel	Visits	Parameters to be analyzed
Hematology and Coagulation	Screening visits and days 35, 77 and 98/EoS	Hemoglobin Hematocrit Erythrocytes (red blood cell) Leukocytes (white blood cell) Differential white blood cell Platelets Prothrombin time (PT) and International normalized ratio (INR) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Reticulocytes
Abbreviated Biochemistry	Weekly starting at randomization except for days 35, 77 and 98/EoS	Chloride Creatinine Cystatin-C Aspartate transaminase (AST) Alanine transaminase (ALT) Blood Urea Nitrogen (BUN) Glomerular Filtration Rate (GFR) calculated using Modification of Diet in Renal Disease (MDRD)
Biochemistry	Screening visits, and days 35, 77 and 98/EoS – Fasting at all visits except for the first screening visit and day 98/EoS	Sodium Potassium Calcium Chloride Magnesium Glucose – fasting at screening, randomization and days 42 and 84/EoT Creatine Kinase Creatinine Cystatin-C Alkaline Phosphatase Lactate dehydrogenase (LDH) Aspartate transaminase (AST) Alanine transaminase (ALT) Gamma glutamyl transpeptidase (GGT) Total bilirubin (direct and indirect) Total protein
Table continued on next page		

Panel	Visits	Parameters to be analyzed
Biochemistry *(continued)*	Screening visits, and days 35, 77 and 98/EoS – Fasting at all visits except for the first screening visit and day 98/EoS	Albumin Total cholesterol HDL (only at the second screening and day 77) Triglycerides Uric Acid Blood Urea Nitrogen (BUN) Inorganic phosphate Glomerular Filtration Rate (GFR) calculated using Modification of Diet in Renal Disease (MDRD) HbA1c
Hormones	Randomization and day 84/EoT	Plasma Adrenocorticotropic Hormone (ACTH) Prolactin Thyroid-stimulating hormone (TSH; only at Screening and EoT)
Serology	Screening	Hepatitis B surface antigen (HBsAg) Hepatitis A virus antibodies (immunoglobulin M) (anti-HAV [IgM]) Hepatitis C (HCV) Antibody
Urinalysis	Screening visits and days 35, 77 and 98/EoS	Leucocytes Nitrite Protein Glucose pH Blood Urobilinogen Bilirubin Ketones Potassium
Drug Screen (urine collection/urine dip stick)	Screening, randomization and day 84/EoT	Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Opioids
Alcohol screen (urine)	Screening, randomization and day 84/EoT	Alcohol
Serum Pregnancy test (for females of child-bearing potential only)	Screening visit and days 84/EoT and 98/EoS	Serum beta human chorionic gonadotropin (β-HCG)
Urine Pregnancy test (for females of child-bearing potential only)	Randomization and day 42	Urine beta human chorionic gonadotropin (β-HCG)

EoS: end-of-study; EoT: end-of-treatment

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician. Unscheduled tests or a repeat of abnormal laboratory test(s) may be performed if clinically indicated and to follow-up on suspected AEs.

The analyses on hematology and coagulation, biochemistry, serology and urinalysis samples will be performed by a central laboratory. Kits from the central laboratory will be provided to the sites to perform urine pregnancy tests on females of child-bearing potential. Results will be noted in the subject's chart.

5.4.4 Physical Examination

The subject will be examined by a principal investigator or qualified delegate at screening, randomization (predose), and days 42 and 84/EoT. Physical examination may also be performed at unscheduled visits if necessary. It includes examination of main body systems, such as abdomen, central nervous system and musculoskeletal system.

The principal investigator or qualified delegate will conduct the exam, determine findings and assess any abnormalities as to clinical significance and whether any exclusion criteria have been met. After study drug administration, new abnormal findings or a worsening of an ongoing abnormal condition must be recorded as an AE.

5.4.5 Electrocardiogram

A 12-lead ECG will be performed at screening, randomization, and day 42 and 84/EoT visits. All ECGs should be taken before any scheduled blood draws. ECGs will be recorded with the subject in the supine position, after the subject has been lying down for approximately 5 minutes. There should be at least 5 minutes between ECG measurements in case a repeat is needed. Any clinically significant adverse changes on the ECG will be reported as AEs. Printouts of all ECGs, marked with the subject number and initials, visit date and visit number should be stored in the subject's source data.

5.4.6 Metabolic Parameters

Metabolic parameters (waist circumference, cholesterol, triglycerides, HDL [the second screening visit and day 77], fasting glucose and weight) and HbA1c will be measured at both screening visits, and at days 35 and 77 visits.

5.4.7 Sponsor Consult on Concomitant Medications

The principal investigator or qualified delegate or allied health professional will consult with the Astellas medical monitor or designee at screening on the concomitant medication history for the subject to confirm no excluded medications are listed. If any changes were made to medications between the screening and randomization visits, the site will contact the medical monitor for a second consult. The consultation will be documented by worksheet.

5.4.8 Columbia Suicide Severity Rating Scale

The C-SSRS [Posner et al, 2009] was developed as a screening tool to identify suicide risk. The interview asks subjects detailed questions regarding suicidal ideation, behaviors, intensity of ideation, and attempts. Response options and recall periods vary in accordance with the nature of the question.

The C-SSRS will be performed by trained site staff via interview at screening, randomization, at all subsequent study visits. At the first screening, the "Lifetime" version is to be used to

determine eligibility. During all subsequent visits, including the second screening visit, the "since last visit" version is used to monitor on-study suicidal ideation and behavior after the initial assessment. Responses will be reported on the tablet. When possible continuity of raters should be maintained across scales for each patient.

Subjects who have a history of suicide attempt or suicidal behavior within the last 12 months, or has suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation domain), will be excluded.

5.4.9 Abnormal Involuntary Movement Scale

The AIMS [Rush, 2000] aids in the early detection of tardive dyskinesia, as well as providing a method for on-going surveillance. The AIMS is a checklist and uses a 5-point rating scale for recording scores for 7 body areas: face, lips, jaw, tongue, upper extremities, lower extremities and trunk. The assessments will be performed by the principal investigator or qualified delegate on the tablet at randomization and day 42 and 84/EoT visits. When possible continuity of raters should be maintained across scales for each patient.

5.4.10 Simpson Angus Scale

The SAS [Simpson & Angus, 1970] is a 10-item scale used to rate adverse neurological effects of antipsychotic medications more broadly. It involves direct observation and a brief neurological examination. Rating requires the investigator to observe the patient's gait and check for tremor, excessive salivation and rigidity in the arms, shoulder and neck. Each item is rated from 0 to 4 and a total score can be obtained. Assessments will be performed by the principal investigator or qualified delegate on the tablet at randomization and day 42 and 84/EoT visits. When possible continuity of raters should be maintained across scales for each patient.

5.4.11 Barnes Akathisia Rating Scale

The BARS [Barnes, 1989] is a rating scale that is used to assess the severity of drug-induced akathisia. The assessments will be performed by the principal investigator or qualified delegate on the tablet at randomization and day 42 and 84/EoT visits. When possible continuity of raters should be maintained across scales for each patient.

5.4.12 Safety Narrative Plan

In addition to typical narratives regarding SAEs and study discontinuation due to TEAEs, subject narratives will describe potential signs of abuse. For more details, refer to Appendices 12.7 and 12.8. Please pay attention to the first page of Appendix 12.7, which includes many of the more specific terms with a higher probability of being related to potential signals of abuse. The remainder of Appendix 12.7 deals with less specific terms that also increase the sensitivity of picking up potential signs of abuse.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent and will be collected until 28 days after the last dose of study drug.

5.5.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, which is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as a serious adverse event or an adverse event ([S]AE).

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to [Appendix 12.3 Liver Safety Monitoring and Assessment] for detailed instructions on Drug Induced Liver Injury (DILI). Abnormal values in AST and/or ALT concurrent or with abnormal elevations in total bilirubin that meet the criteria outlined in [Appendix 12.3 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an (S)AE:

- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

5.5.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to Study Drug

The investigator is obligated to assess the relationship between the study drug and the occurrence of each (S)AE. The investigator will use clinical judgment to determine the relationship. The investigator should also use the Investigator's Brochure (IB). The investigator is requested to provide an explanation for the causality assessment for each SAE and must document this on the SAE worksheet. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider**

that there is a reasonable possibility that the event may have been caused by the study drug".

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
    - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information.

5.5.4 Criteria for Defining the Severity of an Adverse Event

The investigator will use the following definitions to rate the severity of each AE:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.5.5 Reporting of Serious Adverse Events

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue to 28 days after the last dose of study drug.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit a SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness).

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/Special Situations Worksheet to:

Astellas Pharma Global Development – United States
Pharmacovigilance
Fax number 888-396-3750
Alternative Fax 847-317-1241
Email: safety.us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's Medical Monitor/Study Physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/Special Situation Worksheet and on the (e)CRF.

The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness criteria),
- Causal relationship to the study drug (including reason), and
- The drug provided (if any)

The sponsor or sponsor's designee will submit expedited safety reports (e.g., Investigational New Drug [IND] Safety Reports, CIOMS-I) to Competent Authorities (CA) and concerned Ethics Committee per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/local Independent Ethics Committee (IEC) within timelines set by regional regulations (e.g., European Union [EU], electronic Common Technical Document, FDA) where required. Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs which require submission per local requirements of the IRB.

The investigators should provide written documentation of IRB notification for each report to the sponsor.

The investigator may contact the sponsor's Medical Monitor/Study Physician for any other problem related to the safety, welfare, or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol defined AE collection period [see Section 5.5.1 Definition of Adverse Event], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.5.7 Special Situations

Certain Special Situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug, comparator, or background therapy) are collected in the eCRF, as Protocol Deviation per [Section 8.1.6 Protocol Deviations] or may require special reporting, as described below. These Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in the eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the SAE worksheet.

The Special Situations are:

- Pregnancy
- Medication Error, Overdose and “Off label use”
- Misuse/abuse
- Occupational exposure
- Suspected Drug-Drug interaction

5.5.7.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 28 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Section 5.5.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 90 days from the

discontinuation of dosing and report the information to the sponsor according to the timelines in Section 5.5.5 Reporting of Serious Adverse Events using the Pregnancy Reporting Form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per Section 5.5.5 Reporting of Serious Adverse Events. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.5.7.2 Medication Error, Overdose and “Off-Label Use”

If a Medication Error, Overdose or “Off label Use” (i.e., use outside of what is stated in the protocol) is suspected, refer to Section 8.1.6 Protocol Deviations. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in Section 5.5.5 Reporting of Serious Adverse Events together with the details of the medication error, overdose or “Off-Label Use.”

In the event of suspected ASP4345 overdose, the subject should receive supportive care and monitoring. The Medical Monitor should be contacted as applicable.

5.5.7.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in Section 5.5.5 Reporting of Serious Adverse Events together with details of the misuse or abuse of the study drug(s).

5.5.7.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the study drug(s) of site staff whilst preparing it for administration to the patient) to the study drug(s) occurs, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.5.7.5 Suspected Drug-Drug Interaction

If a suspected drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in Section 5.5.5 Reporting of Serious Adverse Events together with details of the suspected drug-drug interaction.

5.5.8 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated informed consent form in order to continue in the clinical study.

5.6 Test Drug Concentration

Pharmacokinetic trough samples will be collected at 4 visits: prior to dosing at days 7, 14 or 21, 42 and 84. Additional samples will be collected at approximately 2 hours and 4 hours post dose on day 42. Subjects should be reminded not to dose at home prior to their clinic visit.

Details on sample collection, processing, labeling, storage, and shipment procedures are provided in the laboratory manual. Analysis will be performed using a validated liquid chromatography with tandem mass spectrometry method at a bioanalytical laboratory specified by the Sponsor. The remainder of the pharmacokinetic samples might be used in the future to explore the absorption, distribution, metabolism and excretion profile, mode of action and/or safety signals of ASP4345. The samples will be destroyed maximally 5 years after clinical study completion.

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood Sample for the Analysis of Antipsychotics

Pharmacokinetic trough samples will be collected at 3 visits: prior to dosing at days 1, 42 and 84. Subjects should be reminded not to dose at home prior to their clinic visit for days 42 and 84.

Details on sample collection, processing, labeling, storage, and shipment procedures will be provided in the laboratory manual.

5.7.2 Blood Sample for the Analysis of Genes Related to Pharmacokinetics, Efficacy, and Safety (Optional)

Knowledge of polymorphisms of genes COMT, and dopamine D_1 and D_3 receptors may help understand and/or explain observed differences in pharmacokinetic profiles, efficacy and safety of ASP4345. After randomization (see schedule of assessments), a 2 mL whole blood sample for the analysis of these genes will be collected. For detailed sample collection, sample labeling and sample shipment procedures refer to the laboratory manual.

5.7.3 Blood Sample for Future Pharmacogenetic Analysis (Retrospective Pharmacogenetic Analysis) (Optional)

A pharmacogenetic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After randomization (see schedule of assessments), a 4 mL sample of whole blood for possible retrospective PGx analysis will be collected. Samples will be shipped to a sponsor designated banking clinical research organization (CRO).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.5 Retrospective PGx Sub-study] for further details on the banking procedures.

5.7.4 Rater Training and Quality Assurance

A centralized rater training and certification program will be used to ensure consistency with the study conventions for the scales. Video and/ or audio monitoring will be conducted to review inter-rater and intra-rater reliability.

5.7.5 Cognitive Training for the Subject

During the randomization visit the subject will be given access to a mobile application designed to provide cognitive training through pre-determined exercises. The application will be uploaded onto the subject's phone once internet and/or cellular service is confirmed. If these capabilities are not available on the subject's phone or they do not own a phone, a hand-held device will be supplied.

This cognitive training is being used in an attempt to provide a standardized background of cognitive engagement for all the subjects. Multi-center trials for this type of cognitive training have revealed minimal if any effect of the cognitive training by itself. Given that ASP4345 is a dopamine D1 receptor PAM, the expectation is that the cognitive training may interaction with pharmacological allosteric modulation of the dopamine D1 receptor.

The subject will be instructed to access the system 4 times per week (each session will have 12 levels to complete and will take approximately 25-45 minutes) throughout the study. The site will familiarize the subject on accessing and using the application. Compliance will be

monitored by the site at each weekly visit as well as between the visits as needed. The subject should be reminded to continue use of the application during weekly visits; however, lack of compliance with these instructions will not be considered a protocol deviation. If the subject has not been compliant it is recommended that the subject complete cognitive training prior to leaving the site. An interim follow up phone call to remind those subjects not compliant with training is also recommended prior to the next visit. Data are automatically transmitted to a central database. Training task performance will be assessed prior to the start of cognitive training and again after the last cognitive training with a standardized task assessment to evaluate improvement.

5.7.6 Virtual Monitoring of Study Drug Compliance

Subjects will be trained during the randomization visit on use of the mobile application for virtual monitoring of study drug compliance. The application will be uploaded onto the subject's phone once internet and/or cellular service is confirmed. If these capabilities are not available on the subject's phone or they do not own a phone, a hand-held device will be supplied. The site will provide training on use of the application, which includes taking a video of themselves dosing the study drug. Subject's will be counseled that accurate and consistent use of the application is an essential part of their participation in the study. Data are automatically transmitted to a central database.

5.8 Total Amount of Blood

Total amount of blood collected per subject for laboratory specimens is approximately 145.5 mL over a 12-week period.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation from treatment is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Discontinuation Criteria from Study Drug Treatment for Individual Subjects:

- Subject develops unacceptable toxicity
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Subject withdraws consent for further treatment

- Subject remains non-compliant with the protocol based on the investigator's or sponsor's assessment
- Female subject becomes pregnant

Additionally, dosing of a subject will be discontinued in the event that any of the following criteria are fulfilled. The subject will be encouraged to continue in the clinical 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.

If the following finding occurs in 2 consecutive measures within 24 hours study drug should be discontinued:

- ALT or AST ≥ 3 x ULN, or ALT or AST ≥ 2 x ULN and ALT or AST ≥ 5 x baseline value, or total bilirubin (TBL) ≥ 2 x ULN.

These findings will be confirmed by repeat measurements within 48 hours. Generally liver enzymes will be followed by repeated measurements until they return to baseline or stable values.

If any of the following findings occur, the study drug should be immediately discontinued:

- QTcF ≥ 500 ms (confirmed on immediate repeat measurements).
- Serum creatinine increases > 26.52 µmol/L (0.3 mg/dL) in an absolute amount or increases > 1.5-fold greater than the baseline value or serum cystatin C > 2-fold greater than the baseline value for which there is no alternate clinical explanation.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD-US. A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in the SAP will be justified in the CSR.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 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.

7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

For each treatment group, the number and percentage of subjects will be characterized for all randomized subjects and by each analysis set.

7.2.1 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.

7.2.2 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.

7.2.3 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.

7.2.4 Pharmacokinetic 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.

7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height and BMI) will be summarized by treatment group and overall for the FAS, ITT and SAF. Descriptive statistics will be presented with the number of subjects, mean, standard deviation, minimum, median and maximum for continuous variables and frequency and percentage for categorical variables.

7.3.1 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all randomized subjects and for subjects in the SAF by treatment group and overall. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented for all randomized subjects by treatment group and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be presented in a listing.

7.3.2.1 Analysis of Antipsychotic Trough Levels

Antipsychotic trough levels on days 1, 42 and 84 will be provided in a listing. Additional data presentations or listings may be specified in the SAP.

7.3.3 Medical and Psychiatric History

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

7.4 Analysis of Efficacy

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.

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

Primary and secondary efficacy endpoints will be summarized at each visit by treatment group.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

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). The primary endpoint of change from baseline in MCCB neurocognitive composite score will be analyzed using a Mixed Models Repeated Measures (MMRM) approach. The model will contain terms for treatment group, pooled site, visit, and treatment by visit, with the MCCB score at baseline used as a covariate. Least squares (LS) means (± standard error [SE]) and 2-sided 90% CIs for the LS mean treatment differences between each dose of ASP4345 and placebo will be presented for the primary endpoint. There will be no adjustment made for multiple comparisons. The primary analysis will use the FAS.

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

7.4.1.2 Sensitivity Analysis

Sensitivity analyses of the primary efficacy endpoint and selected secondary/exploratory endpoints will be performed based on duration since the first psychotic break, smoking status, treatment compliance, and sex. Planned sensitivity analyses will be described in detail in the statistical analysis plan.

7.4.2 Analysis of Secondary 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. 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 for the primary endpoint. There will be no adjustment made for multiple comparisons.

See Section 7.6 Analysis of Pharmacokinetics for description of analysis of pharmacokinetic secondary endpoints.

7.4.3 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 only for the subjects who have at least 1 negative symptom of moderate severity
- Change from baseline to week 12/EoT for the MCCB composite score
- Change from baseline to week 12/EoT for each of the MCCB domains
- Change from baseline to week 12/EoT for the PANSS
- 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 and summary statistics will be provided, by treatment group and overall as specified in the statistical analysis plan.
- COMT and dopamine D_1 and D_3 receptor genotyping

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

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

7.5 Analysis of Safety

7.5.1 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.

The number and percentage of subjects with treatment-emergent AEs, SAEs, AEs leading to withdrawal of treatment, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

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.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline for subjects in the SAF by treatment group and time point.

Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and visit.

7.5.4 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.

7.5.5 Routine 12-lead Electrocardiograms

Descriptive statistics will be used to summarize the ECG parameter results and changes from baseline by treatment group and time point.

7.5.6 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.

7.5.7 Movement disorder (Abnormal Involuntary Movement Scale)

Number and percentage of subjects in each rating category, as well as changes from baseline, will be summarized for each of the items of the AIMS by treatment group and visit.

7.5.8 Simpson Angus Scale

Number and percentage of subjects in each rating category, as well as changes from baseline, will be summarized for each of the items of the SAS by treatment group and visit.

7.5.9 Barnes Akathisia Rating Scale

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

7.6 Analysis of Pharmacokinetics

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.

7.6.1 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.

7.7 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.1.6 Major Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

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

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

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

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

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

This section is not applicable for this study.

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

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

Subjects who do not receive the study drug to which they have been randomized will be analyzed as treated.

See the SAP for details of the definition for windows to be used for analyses by visit.

Sites that do not enroll a sufficient number of subjects will be pooled for analyses by site. The pooling decisions will be made and documented prior to study hard-lock.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at a central laboratory. Central laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The Central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

All procedures conducted under the protocol must be documented. For screen failures, the minimum demographic data (sex, birth date, race and informed consent date), outcome of eligibility assessment (inclusion and exclusion criteria), reason for screen failure and AEs details must be documented.

The investigator or designee will be responsible for eCRF completion and that all data and queries are accurate, complete and are verifiable with the source. The source should be appropriately maintained by the clinical unit.

Electronic data sources and any supporting documents should be available for review/retrieval by the sponsor/designee at any given time.

Clinical Outcome Assessments and Electronic Clinical Outcome Assessments:

Subject clinical outcome assessments for the MCCB and UPSA-2-ER will be completed on a paper copy of the licensed instrument at the site by the principal investigator or qualified delegate. Data will be entered into a database by the vendor following scoring and transmitted to the sponsor.

Subject electronic clinical outcome assessments for the PANSS, NSA-16, C-SSRS, AIMS, SAS, BARS and CGI-S will also be completed by the principal investigator or qualified delegate on an electronic tablet. The completed information will be automatically uploaded into a central website.

All COA data will be transferred electronically to the sponsor at predefined intervals during the study. The vendor will provide the sponsor with a complete and clean copy of the data.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates

- Medical history and physical examination details
- Key efficacy and safety data as specified in the protocol
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Details of dispensing and return of study drug
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)
- Pharmacokinetic sample processing and storage history, including date/time each sample is transferred to the freezer, freezer identification and the temperature log for the freezer (if applicable)

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents [refer to Section 8.1.2 Specification of Source Documents] when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Data Science department of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Dictionary, respectively.

8.1.6 Major Protocol Deviations

A major protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The major protocol deviation criteria are 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.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a major deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file.

8.1.7 End-of-Trial in All Participating Countries

The end of the study is defined as the last visit or follow-up contact of the last subject in the study.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board/Independent Ethics Committee/Competent Authorities

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible ethics committees and regulatory agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any

changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for Astellas Pharma Europe B.V./Astellas Pharma Europe Ltd-sponsored studies within 1 year after last subject out or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their informed consent form (ICF) and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated

ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then sponsor shall serve as the controller of such data, as defined by the European Union (EU) Data Protection Directive, and Investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data If sponsor is not based in the EEA, sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory

agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- Investigator's Brochure (and amendments, where applicable)
- eCRFs
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54
- Signed and dated FDA form 1572
- Signed Investigator's Statement in this protocol and eCRF
- Current Curricula Vitae of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

The investigator will archive all study data (e.g., subject identification code list, source data, CRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA is approved or if the IND is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

All data will be entered on the CRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval

or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new informed consent must also be forwarded to the sponsor.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee

This section is not applicable for this study.

10.2 Other Study Organization

This section is not applicable for this study.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

These lists are not exhaustive. Medications should be considered excluded if taken alone or as part of a combination product. **If in doubt, please contact the Medical Monitor.**

Strong CYP3A inhibitors (> 5-fold increase in AUC)	
indinavir/RIT	Ketoconazole
tipranavir/RIT	Itraconazole
Ritonavir	Voriconazole
cobicistat (GS-9350)	Posaconazole
Indinavir	Telithromycin
Nelfinavir	Troleandomycin
Saquinavir	Clarithromycin
elvitegravir/RIT	Conivaptan
saquinavir/RIT	Nefazodone
lopinavir/RIT	Mibefradil
Boceprevir	grapefruit juice DS
Telaprevir	Idelasib
danoprevir/RIT	LCL161
Moderate CYP3A inhibitors (> 2-fold increase in AUC)	
atazanavir/RIT	Diltiazem
Darunavir	Dronedarone
darunavir/RIT	Aprepitant
Atazanavir	Casopitant
Amprenavir	Netupitant
Cyclosporine	Cimetidine
Ledipasvir	Tofisopam
Fluconazole	grapefruit juice
Ciprofloxacin	schisandra sphenanthera
Erythromycin	Lomitapide
Imatinib	ACT-178882
Crizotinib	FK1706
Verapamil	
Potent CYP3A inducers (> 80%)	
Rifampin	Simvastatin
Rifabutin	Atorvastatin
Mitotane	Fluvastatin
Enzalutamide	Rosuvastatin
Phenytoin	Pitavastatin
Carbamazepine	Pravastatin
Avasimibe	Lovastatin
St John's Wort	

AUC: area under the curve; CYP3A: cytochrome P450 3A; DS = double strength; RIT = Ritonavir (it is a combination drug)

12.2 List of Inducers and Inhibitors of CYP2C19, CYP2D6 and CYP1A2

Below is a list of strong and moderate inhibitors and inducers of CYP1A2, CYP2C19 and CYP2D6. These lists are not exhaustive. These medications can be continued if the subject is on a stable dose prior to screening, but cannot be initiated during the study. Medications should be considered excluded if taken alone or as part of a combination product. **If in doubt, please contact the Medical Monitor.**

Enzyme	Inhibitor (Strong and Moderate)	Inducer (Strong and Moderate)
CYP1A2	Enoxacin, Zafirlukast, Methoxsalen, Mexiletine, Oral contraceptives*	Teriflunomide
CYP2C19	Fluoxetine, Ticlopidine	Efavirenz
CYP2D6	Fluoxetine, Paroxetine, Quinidine, Trebinafine, Cinacalcet, Duloxetine, Mirabegron	

*Oral contraceptives are allowed if the subject is on a stable dose prior to screening [refer to Section 5.1.3 Previous and Concomitant Treatment (Medication and NonMedication Therapy)].

12.3 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase [ALP], and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		Total Bilirubin
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and	> 2 × ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and International Normalized Ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the liver abnormality case report form (LA-CRF) that has been developed globally and can be activated for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The

sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" within the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients, and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, is to be entered in the (e)CRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
  - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
  - Ultrasound or other imaging to assess biliary tract disease,
  - Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5) (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause

hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 × ULN ("2 × ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

References

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3.

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.4 Common Serious Adverse Events

The following is a list of SAEs that the sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in [Section 5.5.2 Definition of Serious Adverse Events]. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs." The investigator is required to follow the requirements detailed in [Section 5.5.5 Reporting of Serious Adverse Events].

Serious Adverse Events Associated with Schizophrenia:

- Neuroleptic malignant syndrome
- Worsening of psychosis requiring hospitalization
- Worsening of suicidal ideation

12.5 Retrospective Pharmacogenetics Sub-Study

INTRODUCTION

Pharmacogenetics (PGx) research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one 4 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

PHARMACOGENETICS ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PHARMACOGENETICS SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.6 Clinical Outcome Assessment Scales

4345-CL-0015 Clinical Outcomes Assessment Scales		
Efficacy Scales		
MATRICS Cognitive Consensus Battery (MCCB)	Primary Endpoint	Paper-based test
University of San Diego Performance-based Skills Assessment-2 Extended Range Scale (UPSA-2ER)	Secondary Endpoint	Paper-based test
Positive and Negative Symptom Scale (PANSS)	Exploratory Endpoint	Tablet-based test
Negative Symptom Assessment-16 Scale (NSA-16)	Exploratory Endpoint	Tablet-based test
Clinical Global Impression of Severity Scale (CGI-S)	Exploratory Endpoint	Tablet-based test
Safety Scales		
Columbia Suicide Severity Rating Scale (C-SSRS)	Safety Endpoint	Tablet-based test
Abnormal Involuntary Movement Scale (AIMS)	Safety Endpoint	Tablet-based test
Simpson Angus Scale (SAS)	Safety Endpoint	Tablet-based test
Barnes Akathisia Rating Scale (BARS)	Safety Endpoint	Tablet-based test

12.7 Adverse Events of Interest Related to Abuse

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

Complete Abuse Screening Terms

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 and perception	Perception disturbances	Hallucination	Drug-induced hallucinosis
				Hallucinating
				Hallucination
				Hallucination NOS

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lower Level Term
				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
				Feeling weightless
				Feels awful
				Feels bad
				Feels poorly
				Felt like a zombie
				Floating feeling
				Foggy feeling head
				Funny episode
				Fuzzy
				Fuzzy head

System Organ Class	Higher Level GT	Higher Level Term	Preferred term	Lower Level Term
				Muzzy head
				Neck strange feeling of
				Soft feeling
				Spaced out
				Thick head
				Unstable feeling
				Weird feeling

NEC: not elsewhere classified; NOS: not otherwise specified

12.8 Drug Withdrawal-Related Adverse Events Occurring Following Drug Discontinuation (Preferred Terms; MedDRA 18.0)

	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 site conditions	General system disorders NEC	General signs and symptoms NEC	

	Higher Level GT	Higher Level Term	Preferred Term
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

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Substantial Changes
1. Update Amount of Blood Collected
DESCRIPTION OF CHANGE:
The total amount of blood collected is increased to 145.5 mL.
RATIONALE:
Total amount of blood collected increased due to adding the analysis of antipsychotic trough levels.
2. Update Schedule of Assessments
DESCRIPTION OF CHANGE:
Revise screening visit 2 to day -20 to -7. Clarify a visit window of -1 day at visit 3. Add row for blood sampling for antipsychotic pharmacokinetics at visits 3, 9 and 15/EOT. Add footnotes to list the procedures that are required on days -1, 42 and 84.
RATIONALE:
Screening visit 2 is revised to ensure there is a week in between MCCB assessment performed at second screening visit and Randomization. Added window for visits Day 1, 42 and 84 to allow some assessments to be performed the day prior to alleviate subject burden.
3. Add Blood Samples for Analysis of Antipsychotics
DESCRIPTION OF CHANGE:
Add new section (5.7.1) to the protocol for the collection of blood samples for analysis of antipsychotics.
RATIONALE:
Added blood sample collection for analysis of antipsychotics to measure if subjects are taking their prescribed antipsychotics.
4. Add Analysis of Antipsychotic Trough Levels
DESCRIPTION OF CHANGE:
Add new section (7.3.2.1) to the protocol for the analysis of antipsychotic trough levels.
RATIONALE:
To provide the details on how the antipsychotic analysis will be presented.

Nonsubstantial Changes
1. Update Key Sponsor's Contact Details
DESCRIPTION OF CHANGE:
Replace one of two Medical Monitors/Study Physicians and remove a clinical research contact.
RATIONALE:
This change is made because of a change in study personnel.
2. Revise Preparation for Cognitive and Functional Tests
DESCRIPTION OF CHANGE:
Remove University of California San Diego Performance-based Skills Assessment-2 Extended Range (UPSA-2-ER), Positive and Negative Symptom Scale (PANSS), Negative Symptom Assessment Scale (NSA16) and Clinical Global Impression of Severity Scale (CGI-S) from the list of assessments that must not be performed within 30 minutes of smoking and/or drinking coffee.
RATIONALE:
Smoking and/or drinking coffee do not have an acute impact on these functional assessments, so restricting use is not necessary.
3. Add Clarification for Oral Contraceptives.
DESCRIPTION OF CHANGE:
Add a bullet to clarify that oral contraceptive use is permitted as long as the subject is on a stable dose prior to screening.
RATIONALE:
Clarifying oral contraceptive use is permitted as long as subject is already using the medication prior to study start.
4. Update Demographics
DESCRIPTION OF CHANGE:
Remove highest level of education and handedness from demographics.
RATIONALE:
Removed from protocol since this information will not be collected.

5. Update Procedure for Positive and Negative Syndrome Scale
DESCRIPTION OF CHANGE:
Remove the requirement that states the informant who completes the positive and negative syndrome scale must consent to participate.
RATIONALE:
Minor clarification to the protocol. Informant is provided an information sheet that does not require a signature.
6. Clarify Reporting of Serious Adverse Events
DESCRIPTION OF CHANGE:
Add text to clarify that the collection and reporting of serious adverse events will continue until 28 days after the last dose of study drug.
RATIONALE:
Added text for consistency throughout protocol.
7. Update the List of Inducers and Inhibitors of CYP2C19, CYP2D6 and CYP1A2
DESCRIPTION OF CHANGE:
Modify the list of inhibitors and inducers and note that these medications may be continued if the subject is taking these medications prior to study start.
RATIONALE:
Clarified usage of medications and removed the medications that were also listed in Appendix 12.1 since these medications are excluded and cannot be continued even if already taking them at the beginning of the study.
8. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering, consistency throughout the protocol).
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

IIA. Substantial Changes

5 Treatments and Evaluation *5.8 Total Amount of Blood*
WAS:
Total amount of blood collected per subject for laboratory specimens is approximately 109.5 mL over a 12-week period.
IS AMENDED TO:
Total amount of blood collected per subject for laboratory specimens is approximately **145.5**~~109.5~~ mL over a 12-week period.

V Flow Chart and Schedule of Assessments

Table 1 Schedule of Assessments

WAS:

Period	Screening		Treatment and Observation													Follow-up
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/ EoT	16
Visit Week	-4 to -3	-3 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	14
Visit Day	-28 to -21	-20 to -1	1	7	14	21	28	35	42	49	56	63	70	77	84	98/ EoS
Visit Window				±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±3 days
Informed Consent	X															
Verify Eligibility Criteria	X		X													
Demographics, including Smoking History and use of Cannabis (a), Height, BMI	X															
Weight and Waist Circumference	X		X						X						X	
Medical and Psychiatric History	X		X													
Duplicate Subject Database Check	X															
Mini-International Neuropsychiatric Interview	X															
Sponsor consult on concomitant medications	X		X													
Vital Signs (b)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12 Lead Electrocardiogram (c)	X		X						X						X	
Physical Examination	X		X						X						X	
Pregnancy Test (d, e)	X (d)		X (e)						X (e)						X (d)	X (d)
Urine Drug and Alcohol Test	X		X												X	
Hematology, Biochemistry,Urinalysis	X	X (f)						X (f)						X (f)		X
Abbreviated Biochemistry			X	X	X	X	X		X	X	X	X	X		X	
Serology for Hepatitis Testing	X															
Plasma Adrenocorticotropic Hormone and Prolactin			X												X	
MATRICS Consensus Cognitive Battery (g, h)	X	X	X (g)						X (g)						X (g)	
University of San Diego Performance-based Skills Assessment-2 Extended Range (h)			X												X	

Positive and Negative Syndrome Scale (h)	X		X		X				X						X	
Negative Symptom Assessment-16 Scale (h)	X		X						X						X	
Clinical Global Impression of Severity Scale	X	X	X						X						X	
Randomization			X													
Abnormal Involuntary Movement Scale			X						X						X	
Simpson Angus Scale			X						X						X	
Barnes Akathisia Rating Scale			X						X						X	
Cognitive Training and Study Drug Compliance via mobile applications (j)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Administration and Review (j)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Sampling for ASP4345 Pharmacokinetics (k, l)				X	X				X (k, l)						X	
Pharmacogenetic testing: COMT and dopamine D_1 and D_3 genotyping (m)			X													
Biobanking Sample for Retrospective PGx Analysis (m)			X													
Columbia-Suicide Severity Rating Scale (n)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking Status			X	X	X	X	X	X	X	X	X	X	X	X	X	

(a) Current and former history of smoking and use of cannabis (via smoking or ingestion) will be collected.

(b) Vital signs include body temperature, pulse and sitting or supine blood pressure.

(c) Electrocardiograms should be collected prior to pharmacokinetic sample collection at screening and days 1, 42 and 84/EoT. Prior to performing ECGs, subjects should rest in the supine position for at least 5 minutes. One additional triplicate ECG can be taken on day 1 if the QTcF exceeds the limits in Exclusion Criterion 9.

(d) Serum pregnancy tests will be performed for women of childbearing potential at the screening visit, and on days 84/EoT and 98/EoS.

(e) Urine pregnancy tests will be performed for women of childbearing potential only on days 1, and 42.

(f) Blood samples for glucose should be performed fasting at the second screening visit (baseline for this test), and days 35 and 77.

(g) All MCCB testing following randomization (i.e., days 42 and 84/EoT) should be performed within a 2 hour window of baseline (day 1).

(h) In order to avoid an acute impact of nicotine and caffeine on cognitive and functional testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCB, UPSA-2-ER, PANSS, NSA-16 and CGI-S assessments.

(i) Cognitive Training will consist of a mobile application provided to the subject with instructions to use 4 times per week from randomization through day 84/EoT. The application will be reviewed with the subject at each visit to check compliance. Study drug compliance will also be recorded using a mobile application.

(j) Subjects will begin dose on day 1 of the study following all baseline procedures performed and randomization. At each subsequent weekly visit study drug will be counted for compliance and a new packet dispensed except for day 84/EoT.

(k) Pharmacokinetic trough samples will be collected prior to dosing at days 7, 14 **or** 21, 42 and 84/EoT.

(l) Additional pharmacokinetic samples will be collected at approximately 2 hours and 4 hours post dose on day 42.

(m) The samples for pharmacogenetic testing (COMT and dopamine D_1 and D_3 receptor genotyping) and biobanking for retrospective pharmacogenetic analysis are optional and will be collected at baseline (day 1) prior to dosing.

(n) The version of the C-SSRS to be performed at the first screening visit is the "Lifetime" version and the version of the C-SSRS to be performed on at the second screening visits and on days 1 though day 98/EoS is the "Since Last Visit."

IS AMENDED TO:

Period	Screening		Treatment and Observation													Follow-up
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/ EoT	16
Visit Week	-4 to -3	-3 to -1	0	1	2	3	4	5	6	7	8	9	10	11	12	14
Visit Day	-28 to -21	-20 to -~~7~~	1	7	14	21	28	35	42	49	56	63	70	77	84	98/ EoS
Visit Window			**-1 days (a)**	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days **(b)**	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days **(b)**	±3 days
Informed Consent	X															
Verify Eligibility Criteria	X		X **(a)**													
Demographics, including Smoking History and use of Cannabis (**ca**), Height, BMI	X															
Weight and Waist Circumference	X		X **(a)**						X						X	
Medical and Psychiatric History	X		X **(a)**													
Duplicate Subject Database Check	X															
Mini-International Neuropsychiatric Interview	X															
Sponsor consult on concomitant medications	X		X **(a)**													
Vital Signs (**db**)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12 Lead Electrocardiogram (**ec**)	X		X						X						X	
Physical Examination	X		X						X						X	
Pregnancy Test (**d, ef, g**)	X (**fd**)		X (**ge**)						X (**ge**)						X (**fd**)	X (**fd**)
Urine Drug and Alcohol Test	X		X												X	
Hematology, Biochemistry,Urinalysis	X	X (**hf**)						X						X		X

								(**h~~f~~**)						(**h~~f~~**)		
Abbreviated Biochemistry			X	X	X	X	X		X	X	X	X	X		X	
Serology for Hepatitis Testing	X															
Plasma Adrenocorticotropic Hormone and Prolactin			X												X	
MATRICS Consensus Cognitive Battery (**~~g, h~~ i, j**)	X	X	X (g)						X (**i~~g~~**)						X (**i~~g~~**)	
University of San Diego Performance-based Skills Assessment-2 Extended Range **~~(h)~~**			X												X	
Positive and Negative Syndrome Scale (**a~~h~~**)	X		X **(a)**		X				X **(b)**						X	
Negative Symptom Assessment-16 Scale (**a~~h~~**)	X		X **(a)**						X **(b)**						X	
Clinical Global Impression of Severity Scale	X	X	X **(a)**						X						X	
Randomization			X **(a)**													
Abnormal Involuntary Movement Scale			X **(a)**						X						X	
Simpson Angus Scale			X **(a)**						X						X	
Barnes Akathisia Rating Scale			X **(a)**						X						X	
Cognitive Training and Study Drug Compliance via mobile applications (**~~j,~~ k**)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Administration and Review (**l~~j~~**)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Sampling for ASP4345 Pharmacokinetics (**~~k, l~~m, n**)				X	X				X (**n~~k, l~~**)						X	
Blood Sampling for Antipsychotic Pharmacokinetics			**X**						**X**						**X**	
Pharmacogenetic testing: COMT and dopamine D_1 and D_3 genotyping (**o~~m~~**)			X													
Biobanking Sample for Retrospective PGx Analysis (**o~~m~~**)			X													
Columbia-Suicide Severity Rating Scale (**p~~m~~**)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking Status			X	X	X	X	X	X	X	X	X	X	X	X	X	

(a) **The following assessments can be performed on day 1: Verify Eligibilty Criteria (also day 1), Weight and Waist Circumference, Medical and Psychiatric History Review, sponsor consult on concomitant medications (if changes have occurred), Cognitive Training Mobile Application Set-up, Positive and Negative Syndrome Scale, Negative Symptom Assessment-16 scale, Clinical Global Impression of Severity Rating Scale, Abnormal Involuntary Movement Scale, Simpson Angus Scale, and Barnes Akathisia Rating Scale. ALL other assessments must be performed as listed on day 1.**

(b) The following clinical assessments can be performed the day prior to days 42 and 84 visits: Positive and Negative Syndrome Scale, Negative Symptom

Assessment-16 Scale, Clinical Global Impression of Severity Scale, Abnormal Involuntary Movement Scale, Simpson Angus Scale and Barnes Akathisia Rating Scale. Performing these assessments the day prior to days 42 and/or 84 is optional. All other assessments must be performed as listed on day 42 and day 84.

(c) Current and former history of smoking and use of cannabis (via smoking or ingestion) will be collected.

(~~b~~**d**) Vital signs include body temperature, pulse and sitting or supine blood pressure.

(~~c~~**e**) ~~Electrocardiograms~~ **ECGs** should be collected prior to pharmacokinetic sample collection at screening and days 1, 42 and 84/EoT. Prior to performing ECGs, subjects should rest in the supine position for at least 5 minutes. One additional triplicate ECG can be taken on day 1 if the QTcF exceeds the limits in Exclusion Criterion 9.

(~~d~~**f**) Serum pregnancy tests will be performed for women of childbearing potential at the screening visit, and on days 84/EoT and 98/EoS.

(~~e~~**g**) Urine pregnancy tests will be performed for women of childbearing potential only on days 1~~,~~ and 42.

(f**h**) Blood samples for glucose should be performed fasting at the second screening visit (baseline for this test), and days 35 and 77.

(~~g~~**i**) All MCCB testing following randomization (i.e., days 42 and 84/EoT) should be performed within a 2 hour window of baseline (day 1).

(~~h~~**j**) In order to avoid an acute impact of nicotine and caffeine on cognitive ~~and functional~~ testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCB~~, UPSA-2-ER, PANSS, NSA-16 and CGI-S~~ assessment~~s~~.

(~~i~~**k**) Cognitive Training will consist of a mobile application provided to the subject with instructions to use 4 times per week from randomization through day 84/EoT. The application will be reviewed with the subject at each visit to check compliance. Study drug compliance will also be recorded using a mobile application.

(~~j~~**l**) Subjects will begin dose on day 1 of the study following all baseline procedures performed and randomization. At each subsequent weekly visit study drug will be counted for compliance and a new packet dispensed except for day 84/EoT.

(~~k~~**m**) Pharmacokinetic trough samples will be collected prior to dosing at days 7, 14 **or** 21, 42 and 84/EoT.

(~~l~~**n**) Additional pharmacokinetic samples will be collected at approximately 2 hours and 4 hours post dose on day 42.

(~~m~~**o**) The samples for pharmacogenetic testing (COMT and dopamine D_1 and D_3 receptor genotyping) and biobanking for retrospective pharmacogenetic analysis are optional and will be collected at baseline (day 1) prior to dosing. **ICFs for substudies may be collected prior to day 1 sample collection.**

(~~n~~**p**) The version of the C-SSRS to be performed at the first screening visit is the "Lifetime" version and the version of the C-SSRS to be performed on at the second screening visits and on days 1 though day 98/EoS is the "Since Last Visit."

5 Treatments and Evaluation *5.7 Other Measurements, Assessments or Methods*
ADDED:
5.7.1 Blood Sample for the Analysis of Antipsychotics **Pharmacokinetic trough samples will be collected at 3 visits: prior to dosing at days 1, 42 and 84. Subjects should be reminded not to dose at home prior to their clinic visit for days 42 and 84.** **Details on sample collection, processing, labeling, storage, and shipment procedures will be provided in the laboratory manual.**

7 Statistical Methodology *7.3.2 Previous and Concomitant Medications*
ADDED:
7.3.2.1 Analysis of Antipsychotic Trough Levels **Antipsychotic trough levels on days 1, 42 and 84 will be provided in a listing. Additional data presentations or listings may be specified in the SAP.**

IIB. Nonsubstantial Changes

II Contact Details of Key Sponsor's Personnel	
WAS:	
Medical Monitor/Study Physician:	PPD
Clinical Research Contacts:	PPD

IS AMENDED TO:	
Medical Monitor/Study Physician:	PPD
Clinical Research Contacts:	PPD

IV Synopsis, Study Design Overview and 2 Study Objective(s), Design and Endpoints *2.2.1 Study Design*
WAS:
In order to avoid an acute impact of nicotine and caffeine on cognitive and functional testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCBB, UPSA-2-ER, PANSS, NSA 16 and CGI-S assessments.
IS AMENDED TO:
In order to avoid an acute impact of nicotine and caffeine on cognitive ~~and functional~~ testing, smoking and intake of coffee will not be allowed approximately 30 minutes before the MCCBB~~, UPSA-2-ER, PANSS, NSA 16 and CGI-S~~ assessments~~.~~

5 Treatments and Evaluation *5.1.3 Previous and Concomitant Treatment (Medication and NonMedication Therapy)*
ADDED:
• **Oral contraceptive use is permitted as long as the subject is on a stable dose prior to screening.**

5 Treatments and Evaluation *5.2.1 Demographics including Smoking History*
DELETED:

~~The subject's highest level of education (in years) and handedness will be recorded. In addition, the highest level of education (in years) for the subject's mother and father will also be recorded.~~

5 Treatments and Evaluation
5.3.1.3 Positive and Negative Syndrome Scale

DELETED:

~~The informant must consent to participate.~~

5 Treatments and Evaluation
5.5.5 Reporting of Serious Adverse Events

WAS:

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue to 28 days.

IS AMENDED TO:

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue to 28 days **after the last dose of study drug**.

12 Appendices
12.2 List of Inducers and Inhibitors of CYP2C19, CYP2D6 and CYP1A2

WAS:

Below is a list of strong and moderate inhibitors and inducers of CYP1A2, CYP2C19 and CYP2D6. These lists are not exhaustive. Medications should be considered excluded if taken alone or as part of a combination product. If in doubt, please contact the Medical Monitor**.**

Enzyme	Inhibitor (Strong and Moderate)	Inducer (Strong and Moderate)
CYP1A2	Ciprofloxacin, Enoxacin, Zafirlukast, Methoxsalen, Mexiletine, Oral contraceptives	Phenytoin, Rifampin, Ritonavir, Teriflunomide
CYP2C19	Fluconazole, Fluoxetine, Ticlopidine	Rifampin, Ritonavir, Efavirenz, Enzalutamide, Phenytoin
CYP2D6	Bupropion, Fluoxetine, Paroxetine, Quinidine, Trebinafine, Cimetidine, Cinacalcet, Duloxetine, Mirabegron	

IS AMENDED TO:

Below is a list of strong and moderate inhibitors and inducers of CYP1A2, CYP2C19 and CYP2D6. These lists are not exhaustive. **These medications can be continued if the subject is on a stable dose prior to screening, but cannot be initiated during the study.**

Medications should be considered excluded if taken alone or as part of a combination product. If in doubt, please contact the ~~M~~**m**edical M**m**onitor**.**

Enzyme	Inhibitor (Strong and Moderate)	Inducer (Strong and Moderate)
CYP1A2	~~Ciprofloxacin,~~ Enoxacin, Zafirlukast, Methoxsalen, Mexiletine, Oral contraceptives*****	~~Phenytoin, Rifampin, Ritonavir,~~ Teriflunomide
CYP2C19	~~Fluconazole,~~ Fluoxetine, Ticlopidine	~~Rifampin, Ritonavir,~~ Efavirenz~~,~~ ~~Enzalutamide, Phenytoin~~
CYP2D6	~~Bupropion,~~ Fluoxetine, Paroxetine, Quinidine, Trebinafine, ~~Cimetidine,~~ Cinacalcet, Duloxetine, Mirabegron	

***Oral contraceptives are allowed if the subject is on a stable dose prior to screening [refer to Section 5.1.3 Previous and Concomitant Treatment (Medication and NonMedication Therapy].**

14 SPONSOR'S SIGNATURES