Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 263CS201 / NCT03745820

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Multiple-Dose, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BIIB104 in Subjects With Cognitive Impairment Associated With Schizophrenia (CIAS)

EUDRA CT NUMBER: 2018-003825-27

IND NUMBER: 106,053

DATE: 30 October 2019
Version 4
Final

Supersedes previous Version 3 dated 12 June 2019

SPONSOR SIGNATURE PAGE

Protocol 263CS201 was approved by:

[redacted], MD
[redacted], Ophthalmology, Pain &
New Indications Research Unit
Biogen

[redacted]
Date (DD-Month-YYYY)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SYNOPSIS

Protocol Title:	A Phase 2, Randomized, Double-Blind, Multiple-Dose, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BIIB104 in Subjects With Cognitive Impairment Associated With Schizophrenia (CIAS)
Protocol Number:	263CS201
Version Number:	4
Name of Study Treatment:	BIIB104
Study Phase:	2
Study Indication:	Cognitive impairment associated with schizophrenia
Study Rationale:	This Phase 2 study is being conducted to evaluate the safety and efficacy of BIIB104 (0.15 and 0.5 mg doses) administered orally, twice daily (BID), for 12 weeks in subjects with CIAS who are receiving antipsychotic background therapy.
Rationale for Starting Dose and Maximum Exposure:	A maximum dose of BIIB104 0.5 mg administered BID was chosen to provide exposure within the expected clinically relevant range with mean concentration levels not exceeding stopping limits set for this study. After correction for species differences in plasma protein binding and the safety factor, BIIB104 exposure limits are 8.1 ng/mL for mean C_{max} and 122 ng•h/mL for mean AUC_{24}. This is based on the no observed adverse effect level (NOAEL) for convulsions in the rat, the most sensitive nonclinical species, which is 5× (unbound C_{max}-based) the human mean C_{max} of 8.1 ng/mL. In addition, the NOAEL for intercostal muscle degeneration/regeneration in the rat is 1× (unbound AUC-based) the human mean AUC_{24} of 122 ng•h/mL. The BIIB104 maximum exposure at steady state ($C_{max,ss}$) and $AUC_{24,ss}$ from the top dosing regimen (7.47 ng/mL and 89.5 ng × h/mL) are expected to be in the exposures that have been previously shown to be safe and well tolerated in schizophrenia patients, with approximately 90% of subjects having minimum exposure at steady state ($C_{min,ss}$) equivalent to or greater than predicted clinically efficacious total plasma concentration (C_{eff}) [2.3 ng/mL]. To minimize the overlap in exposure and allow identification of the minimum efficacious dose, a 0.15 mg BID dose was also selected. At steady state, the mean $C_{max,ss}$

from the low dose is expected to be equivalent to $C_{eff,}$ and within the clinically relevant range.

Study Objectives and Endpoints:

The primary objective of the study is to evaluate the efficacy of BIIB104 in subjects with CIAS using the Working Memory Domain of the MATRICS Consensus Cognitive Battery (MCCB).

The primary endpoint that relates to this objective is the change from baseline in the MCCB Working Memory Domain score to Week 12.

Secondary objectives are as follows:

- To evaluate the safety and tolerability of BIIB104 in subjects with CIAS.
- To evaluate the efficacy of BIIB104 in subjects with CIAS on measures of cognition, functioning, and psychiatric symptomology, as measured by:
  - University of California, San Diego Performance Based Skills Assessment–Brief, international version (UPSA-Bi)
  - Schizophrenia Cognition Rating Scale (SCoRS)
  - MCCB
  - Structured Clinical Interview Positive and Negative Syndrome Scale (SCI-PANSS)
  - Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I)

Secondary endpoints are as follows:

- Incidence of adverse events (AEs) and serious adverse events (SAEs) reported during the study, Scale for the Assessment and Rating of Ataxia (SARA), Columbia Suicide Severity Rating Scale (C-SSRS)
- Change from baseline in UPSA-Bi to Week 12
- Change from baseline in SCoRS to Week 12
- Change from baseline in MCCB Composite scores and Individual Domain scores (excluding Working Memory Domain) to Week 12

- Change from baseline in SCI-PANSS total score and subscale scores to Week 12
- Change from baseline in CGI-S to Week 12
- CGI-I at Week 12

[redacted]

Study Design:	This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of BIIB104 in subjects with CIAS.
Treatment Groups:	Subjects will be randomized in a 1:1:1 ratio into 1 of 3 treatment groups. The randomization will be stratified by region. • Placebo group: Up to 73 subjects to receive oral dosing BID with placebo for 12 weeks. • BIIB104 0.15 mg group: Up to 73 subjects to receive oral dosing BID with BIIB104 0.15 mg for 12 weeks. • BIIB104 0.5 mg group: Up to 73 subjects to receive oral dosing BID with BIIB104 0.5 mg for 12 weeks.
Study Location:	This study will be conducted at approximately 80 sites globally.
Number of Planned Subjects:	Approximately 219 subjects are planned to be enrolled, randomized, and dosed in this study.
Study Population:	This study will be conducted in subjects from age 18 to 55 years, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, diagnosis of schizophrenia of at least 2 years' duration as confirmed by the Mini-International Neuropsychiatric Interview (MINI) Version 7.0.2 for Psychotic Disorders. Subjects must have stable disease (e.g., no hospitalizations or worsening symptoms) for at least 12 weeks prior to randomization and must not have any other significant psychiatric comorbid diagnoses. Subjects must also be receiving ongoing maintenance atypical antipsychotic therapy for at least 8 weeks prior to randomization. Detailed criteria are described in Section 8.
Duration of Treatment and Follow-up:	The maximum total duration of study participation for each subject will be approximately 19 weeks, including a screening phase of approximately 5 weeks, a treatment phase of approximately 12 weeks,

and a safety follow-up phase of approximately 2 weeks.

Sample Size Determination: Fifty-one subjects per treatment group will have approximately 80% power to detect a true mean difference of 3.5 in change from baseline MCCB Working Memory Domain score to Week 12 between the treatment and placebo groups. With an assumed drop-out rate of 30%, 73 subjects are required from each group to maintain the 80% power. This power calculation is based on a 2-sided *t*-test assuming equal variance with a final significance level of 0.1, and a standard deviation (SD) of 7. The statistical software EAST 6.3® is used for sample size calculation. The sample size may be re-estimated based on blinded data review and evolving development of this study.

Statistical Methods: Continuous variables will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by timepoint and treatment group. Point estimates and 90% CIs will be provided where applicable.

The primary endpoint is the change in MCCB Working Memory Domain score from baseline to Week 12. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline in MCCB Working Memory Domain score using fixed effects of treatment, visit, treatment-by-visit interaction, baseline Working Memory Domain score, baseline Working Memory Domain score by visit interaction, and region.

The secondary endpoints are defined in Table 6. The population for the analysis will be subjects in the intent-to-treat (ITT) population with a baseline and at least 1 postbaseline value. For all continuous endpoints, an MMRM model will be used to analyze change from baseline to the Week 12 Visit using fixed effects of treatment, visit, treatment-by-visit interaction, baseline, baseline-by-visit interaction, and region. Sensitivity analyses based on different missing mechanisms will also be performed (imputation methods are defined in the statistical analysis plan).

[redacted] The endpoints will be summarized by MMRM model, as well as reported by standard descriptive statistics.

2. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate transaminase
AUC	area under the plasma drug concentration-time curve
AUC_{24}	area under the plasma drug concentration-time curve from 0 to 24 hours
AUC_{inf}	area under the plasma drug concentration-time curve from 0 to infinity
AUC_{last}	area under the plasma drug concentration-time curve from 0 to the time of last measurement
AUC_{tau}	area under the concentration-time curve within a dosing interval
BID	twice daily
BUN	blood urea nitrogen
[redacted]	[redacted]
CGI-I	Global Clinical Impression–Improvement
CGI-S	Global Clinical Impression–Severity
CIAS	cognitive impairment associated with schizophrenia
$C_{b,u}$	unbound brain drug concentration
C_{eff}	efficacious plasma drug concentration
C_{max}	maximum observed plasma concentration
C_{min}	minimum plasma drug concentration
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
$C_{ss,av}$	average steady-state drug plasma concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
EQ-VAS	EuroQol-Visual Analog Scale
ET	early termination

FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
fMRI	functional magnetic resonance imaging
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
[redacted]	[redacted]
ICH	International Council for Harmonisation
ID	identification
IDMC	independent data monitoring committee
IQ	intelligence quotient
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
MAD	multiple ascending dose
MAR	missing at random
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MGH	Massachusetts General Hospital
MHP	mental health professional
MINI	Mini-International Neuropsychiatric Interview for Psychotic Disorders
MMRM	mixed model repeated measures
MTD	maximum tolerated dose
NMDA	*N*-methyl-D-aspartate
NMDAR	*N*-methyl-D-aspartate receptor
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NPI	Neuropsychiatric Inventory
PD	pharmacodynamics
PK	pharmacokinetics
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's correction
RNA	ribonucleic acid
SAE	serious adverse event
SAFER (criteria)	State versus trait, Accessibility, Face validity, Ecological validity, Rule of 3 Ps (pervasive, persistent, and pathological)
SAP	statistical analysis plan
SARA	Scale for the Assessment and Rating of Ataxia
SCI-PANSS	Structured Clinical Interview for Positive and Negative Syndrome Scale
SCID	Structured Clinical Interview for DSM disorders
SCoRS	Schizophrenia Cognition Rating Scale

SD	standard deviation
SFU	safety follow-up
SM	safety margin
TID	3 times daily
[redacted]	[redacted]
UCSD	University of California, San Diego
ULN	upper limit of normal
UPSA-Bi	UCSD Performance-Based Skills Assessment – Brief, international version

3. SPONSOR INFORMATION

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom

Biogen Japan Ltd.
Nihonbashi 1-chome
Mitsui Building 14F
4-1 Nihonbashi 1-chome
Chuo-ku, Tokyo
103-0027 Japan

For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Reference Manual's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

4. INTRODUCTION

BIIB104 (formerly known as PF-04958242 under the previous Sponsor, Pfizer Inc.) is a positive allosteric modulator (potentiator) of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) that represents a mechanistically novel approach to the treatment of cognitive impairment associated with schizophrenia (CIAS).

BIIB104 has been safe and well tolerated in the approximately 300 subjects exposed to date, with no serious adverse events (SAEs) or severe adverse events (AEs). A maximum tolerated dose (MTD) has not been achieved in the 11 completed clinical studies (conducted by Pfizer Inc.) in healthy volunteers, subjects with schizophrenia, and older subjects (55 to 75 years old, inclusive) with presbycusis. BIIB104 has been evaluated at exposures up to its current clinical cap of mean total maximum observed plasma concentration (C_{max}) of 8.1 ng/mL, or one-fifth the no observed effect level (NOEL).

BIIB104 has demonstrated pharmacological activity both functionally (via a functional magnetic resonance imaging [fMRI]-detected reduction in activity in the left inferior parietal cortex of healthy subjects undergoing a cognitive task [Study B1701003]) and behaviorally (via an approximate 20% attenuation of ketamine-mediated disruptions in verbal learning performance in healthy subjects [Study B1701013]). Most recently, exploratory efficacy data in Study B1701017 (multiple ascending dose [MAD]) demonstrated a statistically significant improvement on the MATRICS Consensus Cognitive Battery (MCCB) Working Memory Domain after 2 weeks of dosing (0.475 mg twice daily [BID]) in subjects with schizophrenia. These results are supported by a statistically significant relationship between average plasma BIIB104 concentration at steady state ($C_{av,ss}$) and MCCB Working Memory Domain (change from baseline to Day 14) observed in Studies B1701017 and B1701004 (MAD in subjects with schizophrenia).

Together, these data, which are consistent with the hypothesized and preclinical effects of BIIB104, suggest the potential effectiveness of BIIB104 to improve cognitive function in subjects with CIAS.

4.1. Schizophrenia and Cognitive Defects

Schizophrenia is a chronic, highly debilitating psychiatric disorder with a point prevalence worldwide ranging from 2.7 to 8.3 per 1000 population [Eaton and Chen 2006]. Schizophrenia includes positive symptoms (hallucinations, paranoia, delusions), negative symptoms (apathy, alogia, affective flattening), and cognitive symptoms (deficits in memory, attention, executive function) [Javitt and Laruelle 2006]. At an individual level, almost all patients with schizophrenia have cognitive impairments relative to what would be expected had they never developed schizophrenia [Kremen 2000]. Impaired cognition is now seen as a feature of schizophrenia that precedes, accompanies, and then outlasts a patient's symptoms and medical regimen [Heinrichs 2005]. Measurable deficits in thought and language, perception, memory, and attention appear in vulnerable children long before psychosis appears [Erlenmeyer-Kimling

2000]. Patients experiencing their first psychotic episodes are cognitively impaired, and this impairment is relatively stable over time [Albus 2002]. Studies suggest little or no relation between symptoms and cognitive performance early in the illness, and cognitive deficits remain when symptoms remit in response to treatment [Hughes 2003; Rund 2004]. Thus, neurocognitive deficits do not correlate with positive symptom severity and only modestly correlate with negative symptom severity (r=0.13-0.27) [Keefe 2006].

Effective treatment of cognitive deficits in schizophrenia remains a critical unmet medical need. Current antipsychotic treatments most effectively treat positive symptoms, modestly improve negative symptoms, and have little to no effect on the cognitive deficits [Keefe 2007; Stroup 2006]. Effective treatment of cognitive deficits would enable patients with schizophrenia to live more fulfilling and productive lives in society.

4.1.1. AMPA Receptors and Cognition

BIIB104 is a potent and highly selective AMPAR positive allosteric modulator (i.e., AMPAR potentiator) that represents a mechanistically novel approach to the treatment of CIAS. In response to glutamate, postsynaptic AMPARs produce a rapid membrane depolarization that removes the magnesium block from colocalized *N*-methyl-D-aspartate (NMDA) receptor-gated ion channels and allows calcium influx into the cell [Malinow and Malenka 2002]. The resulting intracellular cascade activates kinases and transcription factors, which induce long-term potentiation and gene expression [Pláteník 2000]. This process, which produces changes in synaptic morphology and strength, is believed to underlie learning and memory [Bliss and Collingridge 1993]. Pharmacologic NMDAR antagonism in healthy humans [Krystal 1994], as well as genetic manipulation of NMDAR in rodents [Mohn 1999], produce cognitive impairment and behavioral effects suggestive of schizophrenia. High-impact AMPAR potentiators, including BIIB104, have been found to significantly attenuate the NMDAR antagonist-induced cognitive disruptions in these preclinical [Kiss 2013; Roberts 2010; Shaffer 2018; Shaffer 2013; Shaffer 2015] and clinical [Ranganathan 2017; Shaffer 2018] models. Furthermore, postmortem studies have found decreased hippocampal AMPAR density in patients with schizophrenia versus age-matched controls, suggesting some of the strongest evidence for dysregulation of glutamatergic transmission in schizophrenia [Meador-Woodruff and Healy 2000].

Unlike orthosteric agonists, AMPAR potentiators lack intrinsic activity. However, in the presence of glutamate, they augment agonism by modulating the biophysical properties of the receptor. It has been demonstrated that AMPAR potentiators binding at different allosteric sites can attenuate either receptor deactivation (increasing synaptic current amplitude) or both receptor deactivation and desensitization (increasing and prolonging synaptic current). Distinctive modes of allosteric activation are possible as indicated by experiments demonstrating that potentiators can differentially affect receptor deactivation and desensitization to enhance receptor signaling [Partin 1996].

A diverse array of chemotypes, distinguished by their receptor interactions, have been reported to potentiate AMPARs [Grove 2010]. One group of compounds, characterized by the benzamides (e.g., CX516, CX717, and farampator [Org24448, CX691]) and benzothiadiazines (e.g., S18986) [Rosi 2004], attenuate receptor deactivation with minimal-to-modest effects on

receptor desensitization to afford increased amplitude in AMPAR-mediated synaptic currents. These are known as low-impact compounds. Another group of potentiators, exemplified by the biarylpropylsulfonamides (e.g., LY450108 and LY451395) [Jhee 2006] and aminoindane sulfonamides (e.g., GSK729327) [Ward 2011], impede receptor deactivation and desensitization that increases both the amplitude and duration of AMPAR-mediated synaptic currents. Such compounds are classified as high-impact compounds. Based on its common allosteric binding site with biarylpropylsulfonamides like LY451395, along with its electrophysiological properties, BIIB104 is considered a high-impact AMPAR potentiator.

4.1.2. AMPA Potentiators in Clinical Trials

Numerous AMPAR potentiators have been evaluated in humans. The low-impact potentiator CX516, has undergone both small and large clinical trials for its procognitive potential in schizophrenia patients stabilized on concomitant antipsychotics (900 mg three times daily [TID] for 4 weeks) [Goff 2001], in healthy young and elderly subjects [Lynch 1997; Lynch 1996] and in patients with Fragile-X Syndrome (600 mg TID for 1 week + 900 mg TID for 3 weeks) [Berry-Kravis 2006]. Although safe and well-tolerated in these populations, a Phase 2 study of adjunctive therapy in 105 schizophrenic patients (4 weeks of treatment) with CX516 added to clozapine (N = 52), olanzapine (N = 40), or risperidone (N = 13) found no difference from placebo on a composite cognitive score or any cognitive test after 4 weeks or 8 weeks (i.e., 4 weeks after end of treatment) [Goff 2008]. While site methodology was a potential problem (e.g., small size, inadequate dosing duration and/or regimen, potential cognitive battery insensitivity), it should be noted that CX516 is a “low-impact” AMPAR potentiator with a short pharmacokinetic (PK) half-life, which likely also addresses these negative CIAS findings. Single doses of the low-impact potentiator CX717 (300-1,000 mg) have been reported to increase wakefulness and improve performance in sleep-deprived male healthy subjects. CX717 (800 mg twice daily [BID] for 4 weeks) was also reported to be significantly more effective versus placebo on the total Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale (p=0.0024) and on both the hyperactivity (p=0.0168) and inattentiveness (p=0.0273) subscales [Cortex 2006]. CX717 was shown to be efficacious in treating drug induced respiratory depression caused by opioids or certain anesthetics [Business Wire 2008]. In a small clinical trial, a single dose (500 mg) of the low-impact potentiator farampator (Org24448, CX691) improved short-term memory, but impaired episodic memory in elderly subjects [Wezenberg 2007].

More recently, numerous clinical trials have occurred with high-impact AMPAR potentiators. For example, both single (0.25 to 6 mg) and multiple (0.1 mg once daily [QD] for 28 days) doses of GSK729327 were well tolerated in healthy subjects, with no safety issues raised or withdrawals due to AEs [Ward 2011]. Similarly, the high-impact potentiators LY450108 (8 to 30 mg BID for 3 days) and LY451395 (5 to 18 mg BID for 3 days) were studied in patients with probable Alzheimer’s disease [Jhee 2002]. LY450108 was well tolerated at 30 mg BID with dizziness being the most frequent AE; no MTD was determined. LY451395 was well tolerated up to 12 mg BID, but dizziness and nervousness were dose limiting at 15 and 18 mg BID; 15 mg BID was deemed the MTD. Subsequently, the steady-state plasma and cerebrospinal fluid (CSF) concentrations of LY450108 and LY451395 (both at 1 and 5 mg BID for 6 to 8 days) were determined in healthy subjects [Jhee 2006]. All doses were found to be safe and well tolerated in healthy subjects, and both drugs had equivalent unbound plasma and CSF concentrations at

steady-state (i.e., equilibrium at the blood-CSF barrier). LY451395 was then progressed to two separate trials in Alzheimer's disease patients to test its ability to improve the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; 0.2 mg BID for 4 weeks + 1 mg BID for 4 weeks) [Chappell 2007] and the agitation and aggression subscale of the Neuropsychiatric Inventory (NPI-4-A/A; 3 mg BID for 12 weeks) [Trzepacz 2013], respectively. In both studies, patients treated with LY451395 did not show a statistically significant separation from patients taking placebo on the respective primary outcome measures; reported AEs were similar between groups receiving LY451395 and placebo.

Collectively, the reported human safety data for the high-impact potentiators GSK729327, LY450108 and LY451395 have demonstrated good safety and tolerability profiles and are consistent with the historical safety profile of BIIB104, which is considered a high-impact potentiator.

4.2. Current Therapies for CIAS

Currently, there are no approved pharmacological treatments for CIAS.

[redacted]

[redacted]

[redacted]

[redacted]

Additional information about BIIB104 may be found in the Investigator's Brochure.

4.4. Study Rationale

The purpose of this Phase 2 study is to evaluate the safety and efficacy of BIIB104 0.15 and 0.5 mg administered orally, BID, for 12 weeks in subjects with CIAS who are receiving antipsychotic background therapy.

[redacted]

5. SCHEDULES OF ACTIVITIES

Study activities for the Screening and Treatment Periods are presented in Table 3 and Table 4, respectively. [redacted]

The Investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 3: Schedule of Activities – Screening

Study Phase:	**Screening**	
Protocol Activity	**Screening Visit 1 (Day -35 to Day -8)**[1]	**Screening Visit 2 Placebo Lead-In (7-day Placebo Lead-In must begin between Day -9 and Day -7, inclusive)**[14]
Informed Consent Form	X	
Informant Consent Form[2]	X	
Validated Reading Test	X	
Demographics	X	
Site Inclusion/Exclusion Criteria Verification	X----------	
Sponsor Inclusion/Exclusion Criteria Verification and Confirmation[3]	X----------	
Independent Telemedicine Review (SAFER)[4]	X	
Medical, Neurological, Psychiatric, and Medication History	X	
MINI 7.0.2 Diagnostic Interview	X	
SCI-PANSS[1]	X	
C-SSRS[5, 6]	X	X
Study Guidelines Review[7]	X	X
Contraception Check[8]	X	X
Concomitant Psychiatric Medication Check[6]	X	X
Height[6]	X	
Weight[6]	X	
Full Physical and Neurological	X	

Study Phase:	**Screening**	
Protocol Activity	**Screening Visit 1 (Day -35 to Day -8)[1]**	**Screening Visit 2 Placebo Lead-In (7-day Placebo Lead-In must begin between Day -9 and Day -7, inclusive)[14]**
Examinations[6]		
SARA[6]	X	
12-Lead ECG, Triplicate[6]	X	
Vital Signs (temperature, supine blood pressure, pulse rate, respiratory rate)[6]	X	X
Laboratory Tests		
Urine Drug and Alcohol Test[6]	X	
Serum Pregnancy Test[6, 9]	X	
Serum FSH[6, 10]	X	
Clinical Safety Laboratory Tests (hematology, blood chemistry, and urinalysis)[6, 11]	X	
Antipsychotic Blood Sampling	X	
Assessments		
MCCB[1, 12]	X	
[redacted]		
CGI-S	X	
Placebo Lead-In Training		X
Dispense Lead-In Product Supply		X
Dispense Phone or Phone Application		X
Phone Application Training[13]		X
Serious Adverse Event Reporting	X----------	
Concomitant Therapy and Procedures Recording[6]	X	X

[redacted]; CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; FSH = follicle- stimulating hormone; [redacted]; MCCB = MATRICS Consensus Cognitive Battery; MINI 7.0.2 = Mini-International

Neuropsychiatric Interview Version 7.0.2 for Psychotic Disorders; PANSS = Positive and Negative Syndrome Scale; SAFER = State versus trait, Accessibility, Face validity, Ecological validity, Rule of 3 Ps (pervasive, persistent, and pathological); SARA = Scale for the Assessment and Rating of Ataxia; SCI-PANSS = Structured Clinical Interview for Positive and Negative Syndrome Scale; [redacted].

[1] The MCCB, [redacted], and SCI-PANSS assessments must be completed over a maximum of 3 out of 5 consecutive working days during the Screening Period.

[2] Informant consent must be signed prior to the in-person informant interview conducted during the Screening Period. Informant interview must be conducted in person (but does not have to be performed at study site) during the same 3-day window allowed for the associated subject's screening SCI-PANSS. Informant interview may be conducted by telephone for all other study visits as long as it is within the relevant visit window. The informant will provide input for completing study rating scales (e.g., Informant Questionnaire for PANSS, SCoRS).

[3] Site will complete a pre-randomization form for subjects who meet the screening requirements. Randomization may not proceed without Sponsor approval. See Study Reference Manual.

[4] Scheduled after completion of on-site visit and site confirmation of initial eligibility. See Study Reference Manual for details.

[5] C-SSRS "Lifetime" evaluation will be conducted at the first Screening Visit. C-SSRS "Since Last Visit" evaluation will be conducted at all other timepoints.

[6] The following safety assessments should, whenever possible, be completed in the following order: C-SSRS, concomitant medications, height, weight, physical examination, neurological examination, SARA, 12-lead ECG, supine blood pressure and pulse rate, urine drug and alcohol screening, blood/urine specimens.

[7] See Section 8.3 and the Study Reference Manual for additional information.

[8] All women of childbearing potential and all men. Subjects should be reminded of requirement to use a highly effective method of contraception throughout the study and for 30 days after the last dose of assigned treatment.

[9] Women of childbearing potential only.

[10] Collected only in females who have been amenorrheic for at least 12 months to confirm postmenopausal status.

[11] Whenever possible, screening laboratory values should be taken following at least a 4-hour fast.

[12] The screening efficacy assessments should, if possible, be completed in the following order: MCCB, [redacted], CGI-S. The MCCB, [redacted] should preferably be completed during a single screening day; subjects can take breaks between assessments. If the rater determines that MCCB and additional cognitive assessments cannot be completed the same day, such assessments can be continued the next day. However, the [redacted] assessments must be administered on the same day as their respective immediate recall assessments (contained in the MCCB). See Study Reference Manual for additional details.

[13] A smart phone application will be used to collect study data (e.g., compliance check). Subjects may use their own phone for phone applications, or a phone can be provided for the duration of the study.

[14] The 7-day Placebo Lead-In evaluation may begin any time after eligibility has been established based on Screening assessments, provided that the Placebo Lead-In is completed no earlier than 3 days prior to the Baseline/Day 1 Visit.

Table 4: Schedule of Activities – Placebo-Controlled Treatment and Safety Follow-Up

Study Phase:	**Baseline**	**Treatment**							**SFU**
Protocol Activity	**Day 1**[1]	**Week 1/ Day 8**[2]	**Week 2/ Day 15**[1, 2]	**Week 4/ Day 29**[2]	**Week 6/ Day 43**[1, 2]	**Week 8/ Day 57**[2]	**Week10 / Day 71**[2]	**Week 12/ Day 85**[1, 2] **/ET**[3]	**14 Days After Last Dose**[2]
Inclusion/Exclusion Criteria Review	X[4]								
Randomization	X								
Medical, Neurological, Psychiatric, and Medication History	X								
C-SSRS[5, 6]	X	X	X	X	X	X	X	X	X
Study Guidelines Review[7]	X	X	X	X	X	X	X	X	
Contraception Check[8]	X	X	X	X	X	X	X	X	
Concomitant Psychiatric Medication Check	X	X	X	X	X	X	X	X	X
Weight[6]	X		X	X	X	X		X	
Full Physical and Neurological Examination[6]								X	
Brief Physical and Neurological Examination[6]	X[9, 10]	X[10]	X		X				X
SARA[6]	X[9, 10]	X[10]	X		X			X	X
12-Lead ECG[6]	X[10]	X[10]	X	X	X	X		X	
12-Lead ECG, Triplicate[6]	X								

Study Phase:	**Baseline**	**Treatment**							**SFU**
Protocol Activity	**Day 1[1]**	**Week 1/ Day 8[2]**	**Week 2/ Day 15[1, 2]**	**Week 4/ Day 29[2]**	**Week 6/ Day 43[1, 2]**	**Week 8/ Day 57[2]**	**Week10 / Day 71[2]**	**Week 12/ Day 85[1, 2] /ET[3]**	**14 Days After Last Dose[2]**
Vital Signs (temperature, supine blood pressure, pulse rate, respiratory rate)[6]	X	X	X	X	X	X	X	X	
Laboratory Tests									
Urine Drug and Alcohol Test[6]	X		X		X			X	
Urine Pregnancy Test[6, 11]	X			X		X		X	X
Clinical Safety Laboratory Tests (hematology, blood chemistry, and urinalysis)[6]	X	X	X	X		X		X	X
Antipsychotic Blood Sampling	X							X	
[redacted]									
Subject/Informant-Reported Outcomes									
[redacted]									
Assessments									
MCCB[15]	X		X		X			X	
[redacted]									

Study Phase:	**Baseline**	**Treatment**							**SFU**
Protocol Activity	**Day 1[1]**	**Week 1/ Day 8[2]**	**Week 2/ Day 15[1, 2]**	**Week 4/ Day 29[2]**	**Week 6/ Day 43[1, 2]**	**Week 8/ Day 57[2]**	**Week10 / Day 71[2]**	**Week 12/ Day 85[1, 2] /ET[3]**	**14 Days After Last Dose[2]**
[redacted]									
SCI-PANSS[15, 16]	X		X		X			X	
UPSA-Bi[15]	X							X	
SCoRS[15, 16]	X							X	
CGI-S[15, 17]	X				X			X	
CGI-I[15, 17]					X			X	
Dispense Study Treatment[18]	X	X	X	X	X	X	X		
Monitor Dosing Compliance	X	X	X	X	X	X	X	X	
Study Treatment Administration	Oral dosing BID from Day 1 through Day 85----------								
Adverse Event Recording	X ----------								
Serious Adverse Event Reporting	X ----------								
Concomitant Therapy and Procedures Recording[6]	X ----------								

AE = adverse event; [redacted]; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; ET = Early Termination; h = hours; [redacted]; MCCB = MATRICS Consensus Cognitive Battery; PK = pharmacokinetic; SAE = serious adverse event; SARA = Scale for the Assessment and Rating of Ataxia; SCI-PANSS = Structured Clinical Interview for Positive and Negative Syndrome Scale; SCoRS = Schizophrenia Cognition Rating Scale; SFU = Safety Follow-Up; [redacted]; UPSA-Bi = UCSD (University of California, San Diego) Performance-Based Skills Assessment – Brief, international version.

[1] If needed, cognitive behavioral assessments may be completed over 2 consecutive working days for feasibility and subject comfort. The following efficacy assessments should, whenever possible, be completed in the following order: MCCB, [redacted] SCI-PANSS, UPSA-Bi, SCoRS, CGI-S, CGI-I.
[2] The visit window is ±3 calendar days relative to baseline. The total time between visits is not to exceed 10 calendar days (for Week 2) or 17 calendar days (for all other visits).
[3] Week 12 (Day 85/ET) assessments should be completed in the event of early subject withdrawal/early termination (ET).
[4] The site will review all Screening Visit assessments against the inclusion/exclusion criteria, assess for any changes from screening, and reconfirm eligibility prior to randomization.
[5] C-SSRS "Since Last Visit" evaluation.
[6] The following safety assessments should, whenever possible, be completed in this order: C-SSRS, concomitant medications, weight, physical examination, neurological examination, SARA, 12-lead ECG, vital signs, urine drug and alcohol screening, blood/urine specimens.
[7] See Section 8.3 and the Study Reference Manual for additional information.
[8] All women of childbearing potential and all men must practice effective contraception during the study. After their last dose of study treatment, men and women must continue with contraception for at least 30 days.
[9] To be performed predose for all study sites. For Japanese study sites, see Footnote 10 for additional instructions.
[10] **For Japanese study sites only** (items designated with Footnote 10 are for Japanese sites only unless otherwise specified):

- On Day 1, in addition to baseline assessments, a [redacted] will be collected (see Table 5 for timing) and additional safety evaluations (AE recording, 12-lead ECG, brief neurological examination, and SARA) will be performed 2-hours postdose. Should any abnormal findings arise during these evaluations, an additional [redacted] will be collected. Dosing will be performed under medical supervision, and observation may be extended at the Investigator's discretion prior to discharge from the site, if necessary, including an overnight stay.
- On Day 8, a [redacted] will be collected (see Table 5 for timing), and additional safety assessments 2-hours postdose (AE recording, 12-lead ECG, brief neurological examination, and SARA) will be performed.
- On Day 8, the Investigator will review the available blinded safety data of the subject for Days 1 through 8, including, but not limited to: all available AEs, SAEs, vital signs, ECGs, and clinical assessments. The Investigator will then communicate any abnormal findings to the Biogen Medical Director and Medical Safety Officer (see Section 14.3 for additional details about this Japan-specific safety review).

[11] Women of childbearing potential only.
[redacted]
[13] Whenever possible, complete before other procedures or assessments.
[14] Optional assessment. Will only apply when informant, relative, or caregiver has sufficient contact with the subject to meet the requirements of the assessment tool.
[15] Whenever possible, the MCCB and UPSA-Bi should be administered within the same time period ±2 hours from the Baseline/Day 1 Visit time of assessment for all postbaseline assessments. The MCCB and additional cognitive assessments (i.e., [redacted]) should preferably be completed during a single assessment day; subjects can take breaks between assessments. If the rater determines that MCCB and additional cognitive assessments cannot be completed the same day, they can be continued the next day.

However, the [redacted] assessments must be administered on the same day as their respective immediate recall assessments (contained in MCCB). The same rater should administer these assessments whenever possible. See the Study Reference Manual for additional information.

[16] The informant will provide input for completing study rating scales (e.g., Informant Questionnaire for PANSS, SCoRS). This may be performed remotely (i.e., by phone) after the Screening Visit. See Table 3 and the Study Reference Manual for information about informant consent and interview.

[17] CGI-S and CGI-I scales should be rated after all other study efficacy assessments are completed. The same rater should administer these assessments whenever possible.

[18] Study treatment is to be dispensed after all visit assessments have been completed. The first dose of study treatment will be supervised by the site staff at the Baseline/Day 1 Visit. Study treatment will be administered BID over the course of the study. Antipsychotic background medication will not be administered or provided by the Sponsor or the study site.

[redacted]

6. STUDY OBJECTIVES AND ENDPOINTS

Table 6: Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
The primary objective of the study is to evaluate the efficacy of BIIB104 in subjects with CIAS, using the Working Memory Domain of the MATRICS Consensus Cognitive Battery (MCCB).	The primary endpoint is the change from baseline in MCCB Working Memory Domain score to Week 12.
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of BIIB104 in subjects with CIAS	Incidence of adverse events (AEs) and serious adverse events (SAEs) reported during the study, Scale for the Assessment and Rating of Ataxia (SARA), Columbia Suicide Severity Rating Scale (C-SSRS)
To evaluate the efficacy of BIIB104 in subjects with CIAS on measures of cognition, functioning, and psychiatric symptomology, as measured by:	
• University of California, San Diego Performance Based Skills Assessment–Brief, international version (UPSA-Bi)	Change from baseline in UPSA-Bi assessment to Week 12
• Schizophrenia Cognition Rating Scale (SCoRS)	Change from baseline in SCoRS assessment to Week 12
• MCCB	Change from baseline in MCCB Composite and Individual Domain scores (excluding Working Memory Domain) to Week 12
• Structured Clinical Interview for Positive and Negative Syndrome Scale (SCI-PANSS)	Change from baseline in SCI-PANSS total score and subscale scores to Week 12
• Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I)	Change from baseline in CGI-S to Week 12 CGI-I at Week 12

[redacted]

This clinical study collects samples that under separate optional consent may be used for future scientific and genetic research. Objectives related to this future research have not been determined.

7. STUDY DESIGN

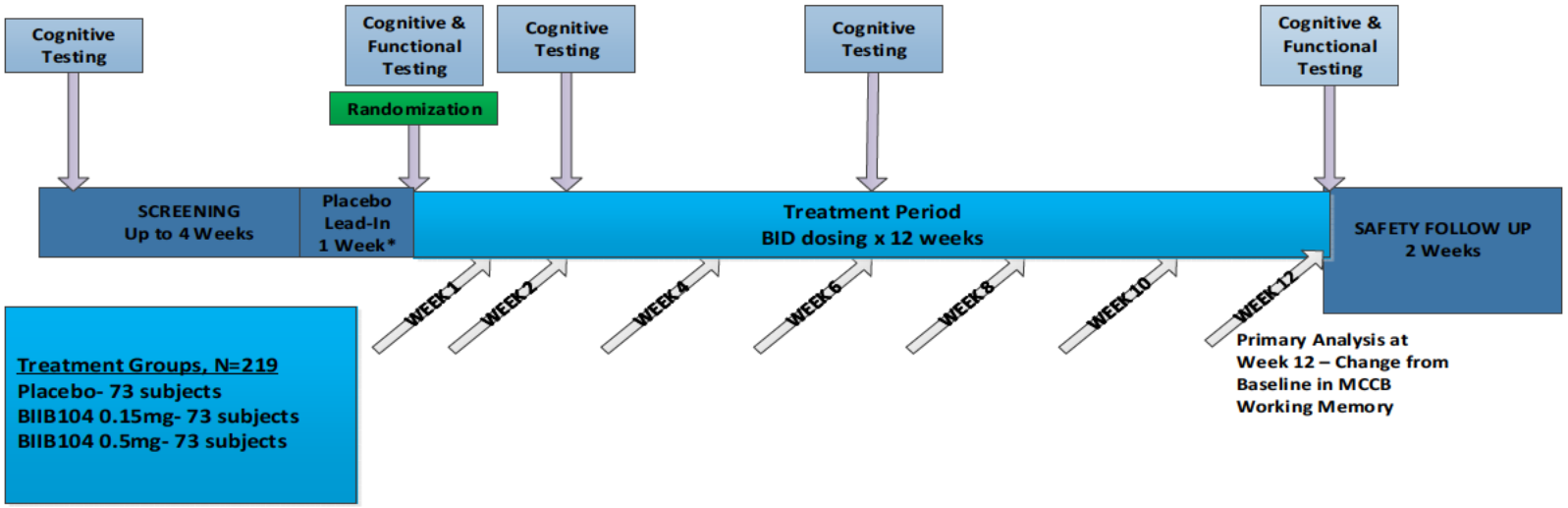
This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of BIIB104 in subjects with CIAS. Approximately 219 male and female subjects with stable schizophrenia from age 18 to 55 years, inclusive, will be recruited. Dosing with BIIB104 0.15 mg BID and 0.5 mg BID versus placebo will be evaluated over a treatment phase of 12 weeks. The study will be conducted at approximately 80 sites globally.

The study includes a screening phase, a placebo lead-in phase, a randomized treatment phase, and a safety follow-up (SFU) phase to begin after the last dose of study treatment. The primary analysis will be conducted after 12 weeks of placebo-controlled treatment.

Screening evaluation will occur up to 35 days prior to randomization. Once eligibility has been established, a 7-day Placebo Lead-In evaluation will be conducted to assess the subject's ability to comply with dosing requirements; this evaluation must be completed no earlier than 3 days prior to the Baseline/Day 1 Visit. After Sponsor reconfirmation of eligibility and completion of baseline measurements at the Baseline/Day 1 Visit, subjects will be randomized in a 1:1:1 ratio to receive BIIB104 0.5 mg, BIIB104 0.15 mg, or placebo (planned for 73 subjects per treatment group). The randomization will be stratified by region. Subjects will be dosed at approximately 12-hour intervals for approximately 12 weeks. Total duration of subject participation will be approximately 19 weeks from screening to final follow-up visit.

See Figure 1 for a schematic presentation of the study design.

Figure 1: Study 263CS201 Schematic



N = number of subjects; MCCB = MATRICS Consensus Cognitive Battery; BID = twice daily.

*Note: The Placebo Lead-In evaluation may begin any time after eligibility has been established based on screening assessments, provided that the Placebo Lead-In is completed no earlier than 3 days prior to the Baseline/Day 1 Visit.

7.1. Study Duration for Subjects

The maximum total duration of study participation for each subject will be approximately 19 weeks including a screening phase of approximately 5 weeks, a treatment phase of approximately 12 weeks, and a safety follow-up phase of approximately 2 weeks.

The end of study date for a subject may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment. If the subject has ongoing AEs that are being followed, the end of study date may be the date of AE resolution.

7.2. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Study Reference Manual. It is recommended that, whenever possible, subjects and informants be interviewed and assessed throughout the study by the same rater. Reasons for changes in certified raters should be documented in the source. The Study Reference Manual provides a detailed description of specific study assessment information.

7.3. Study Stopping Rules

The Sponsor can terminate this study, after informing the Investigator, at any time. The Investigator will be notified by the Sponsor if the study is placed on hold, completed, or closed.

Stopping criteria for a seizure event are as follows:

- The study may be stopped if 1 subject experiences a seizure (postdosing and confirmed following unblinding to be on active study treatment), with a diagnosis of seizure confirmed by an independent panel of neurologists where no other cause has been identified. The process is described as follows:
  - If any subject has a suspected seizure event, individual dosing will be stopped immediately.
  - All available information regarding the seizure event including a Diagnostic Interview for Seizure Identification form will be provided to an independent panel of neurologists for review and adjudication as to the diagnosis and the possible relationship to the blinded study treatment.
  - The Sponsor will provide the outcome of the adjudication to the Independent Data Monitoring Committee (IDMC). If the IDMC recommends terminating the study, the Sponsor will unblind the treatment allocation for the subject who experienced the seizure. The study may be terminated by the Sponsor on recommendation of the IDMC.

The Sponsor and the IDMC will review safety data on an ongoing basis. The study may be modified or terminated based on recommendation of the IDMC or at the discretion of the Sponsor.

7.4. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of randomization, or at the timepoint specified in the individual eligibility criterion listed:

1. Evidence of a personally signed and dated informed consent document at the time of Screening indicating that the subject has been informed of all pertinent aspects of the study.

2. Evidence of a personally signed and dated informed consent for the informant indicating the informant has been informed of all pertinent aspects of the study. Informant consent must be signed prior to the in-person informant interview conducted during Screening.

3. Otherwise healthy male and/or female subjects from age 18 to 55 years, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), diagnosis of schizophrenia of at least 2 years duration as confirmed by the MINI 7.0.2 for Psychotic Disorders. The MINI 7.0.2 for Psychotic Disorders will also be used to exclude comorbid diagnoses. In addition, diagnosis of schizophrenia must be deemed "valid" by remote, independent raters using prespecified criteria (see Section 9.1.1.3).

4. Evidence of stable schizophrenia symptomatology ≥12 weeks (e.g., no hospitalizations for schizophrenia, no increase in level of psychiatric care due to worsening of schizophrenia symptoms).

5. Subjects must be receiving ongoing maintenance atypical antipsychotic therapy (except clozapine), on a stable treatment regimen for ≥8 weeks prior to Baseline/Day 1, including concomitant psychiatric medications. Doses of background atypical antipsychotics should be within the recommended dose range listed in the approved product labeling of the country where the study is being conducted. Doses exceeding the recommended dose range are not permitted and doses below the recommended dose range should be discussed with the Sponsor's Medical Monitor (see Section 11.4.1).

    – Treatment regimen stability is defined as maintaining the same dosage of treatments except for minor adjustments (≤25%) to manage medication-specific tolerability issues. Recognizing that physicians outside of the study may be managing the subject's background antipsychotic and other psychiatric medications, changes in background antipsychotic and psychiatric medications should be discussed with the Sponsor's Medical Monitor.

    – Stable concomitant treatment with a second atypical antipsychotic, at doses that do not exceed the range listed in the approved product labeling of the country where the study is being conducted, is permissible if used for a targeted symptom

(e.g., insomnia) or an adverse effect from the primary maintenance antipsychotic treatment, but not if it is used for refractory psychotic symptoms. Treatment regimen stability as defined above applies to the second antipsychotic. **Subjects should be taking no more than 2 background antipsychotics.**

- Note that hypnotics are an exception to the treatment regimen stability requirement; prohibited hypnotics may be substituted with allowed hypnotics administered as described in Section 11.4.1.

6. Must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

7. Must have an identified informant (e.g., family member, social worker, caseworker, or nurse who interacts [in person or by telephone] with the subject at least 2 times per week) who should, whenever possible, be consistent throughout the study and considered reliable by the Investigator.

8. Must reside in a stable living situation, in the opinion of the Investigator, for at least 12 weeks prior to Screening and be expected to remain in a stable living situation for the duration of the study.

9. Must have oral fluency in the test language confirmed by a standard score of ≥70 at Screening on a validated reading assessment test (please refer to the Study Reference Manual for appropriate reading test). Non-native speakers of the test language must have at least 7 years of formal education in this language.

10. All women of childbearing potential and all men must practice highly effective contraception during the study and for at least 30 days after the last dose of study treatment. For further details of contraceptive requirements for this study, refer to Section 15.5.

11. Body mass index of 17.5 to 45.0 kg/m^2 and total body weight >50 kg (110 lb). Subjects with a BMI >40.5 kg/m^2 must be discussed with the Sponsor's Medical Monitor to determine subject eligibility.

12. SCI-PANSS: No more than moderate-severe rating (score ≤5) on delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution, and hostility (i.e., PANSS, positive symptom items P1, P3, P5, P6, P7), or unusual thought content (G9); and no more than a moderate rating (score ≤4) on conceptual disorganization (P2).

13. At least 80% dosing regimen compliance during the Placebo Lead-In period.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion as listed:

1. Individuals who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or Sponsor employees directly involved in the conduct of the study.

2. Participation in other studies involving treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) prior to randomization and/or during study participation.

3. Participation in a trial that uses any component or version of the MCCB or the UCSD Performance-Based Skills Assessment test within the previous 6 months.

4. Participation in cognitive remediation therapy within 6 months prior to randomization.

5. Participation in ongoing cognitive behavioral therapy that was initiated <8 weeks prior to Baseline/Day 1.

6. Screening MCCB Working Memory Domain T-score ≥60.

7. Current DSM-5 diagnosis of schizoaffective disorder on the MINI 7.0.2 for Psychotic Disorders.

8. Current DSM-5 diagnosis of major depressive episode, manic and hypomanic episode, panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and/or generalized anxiety disorder on the MINI 7.0.2 for Psychotic Disorders.

9. Lifetime DSM-5 diagnosis of antisocial personality disorder, anorexia nervosa, bulimia nervosa, and/or binge-eating disorder on the MINI 7.0.2 for Psychotic Disorders.

10. Meets the DSM-5 diagnosis of moderate or severe substance use disorder (excluding nicotine dependence) within 12 months of screening on the MINI 7.0.2 for Psychotic Disorders interview.

11. DSM-5 diagnosis of Intellectual Disability (intellectual developmental disorder).

12. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

13. Pregnant or breastfeeding female subjects; male subjects with partners who are currently pregnant.

14. Evidence or history of current clinically significant hematological, renal, endocrine (excluding adequately controlled hypothyroidism or hyperthyroidism), pulmonary (excluding chronic bronchitis, mild emphysema or chronic obstructive pulmonary disease), gastrointestinal (including conditions that can affect drug absorption, e.g., gastrectomy), oncological, dermatological, immunological disease, as determined by the Investigator in discussion with the Sponsor. Medical conditions not specifically addressed in this section may be discussed with the Sponsor's Medical Monitor to determine subject eligibility. Note that controlled type 2 diabetes (HbA1c ≤7%) will not be considered a significant medical illness and will not exclude subjects from the study; type 1 diabetes is exclusionary.

15. Evidence or history of current clinically significant cardiovascular disease, including uncontrolled hypertension (standing or supine diastolic pressure >95 mmHg and/or standing or supine systolic pressure >170 mmHg with or without treatment); ischemic heart disease; or uncompensated heart failure, acute myocardial infarction, bypass surgery within 6 months of screening. Controlled essential hypertension and nonclinically significant sinus bradycardia and sinus tachycardia will not be considered significant medical illnesses and would not exclude a subject from the study.

16. History of seizures or of a condition with risk of seizures; as an exception, a history of 1 febrile seizure in childhood will not exclude a subject from the study.

17. Lifetime history of head injury with clinically significant sequelae (e.g., loss of consciousness for >15 minutes).

18. History of hyponatremia, syndrome of inappropriate antidiuretic hormone secretion or psychogenic polydipsia.

19. Treatment with electroconvulsive therapy within the 6 months prior to randomization.

20. History of neuroleptic malignant syndrome as determined by the Principal Investigator with consultation from the Sponsor.

21. Significant extrapyramidal symptoms that have not been stabilized with anticholinergics.

22. Onset of schizophrenia symptoms prior to age 12.

23. Positive urine drug screen for illicit drugs or drugs that cannot be explained by prescribed treatments (however, it should be noted that marijuana is prohibited whether prescribed or recreational).

24. Use of prohibited treatments (see Section 11.4.1) and inability to discontinue these concomitant treatments after the Screening Visit. These treatments must be discontinued (or tapered if medically indicated) for a minimum of 5 half-lives prior to randomization at the Baseline/Day 1 Visit. Note that psychiatric medications (excluding psychiatric medications prescribed for non-psychiatric conditions and hypnotics) cannot be

discontinued to address this criterion due to the treatment regimen stability requirements listed in inclusion criterion 5, above.

25. Use of concomitant treatment that can impair cognition, (e.g., centrally acting antihistamines) as determined by the Investigator in consultation with the Sponsor.

26. Use of concomitant treatment with a significant risk associated with seizures (see Section 11.4.1).

27. Use of typical antipsychotic treatments, including prochlorperazine, haloperidol, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, trifluoperazine, chlorpromazine, and perphenazine. This list is not all inclusive; the Investigator should discuss the use of any concomitant treatment associated with typical antipsychotic treatments with the Sponsor's Medical Monitor prior to randomizing a subject.

28. Use of off-label treatments for schizophrenia (including, but not limited to, donepezil and modafinil).

29. Screening laboratory test results that deviate from the upper or lower limits of the reference range, except for nonclinically significant values, as determined by the Investigator in consultation with the Sponsor's Medical Monitor, including the following:

    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) must be ≤2 times the upper limit of reference range, *and* total bilirubin must be ≤1.5 times the upper limit of the reference range at screening.

    - Impaired renal function at screening (e.g., repeated values of creatinine and blood urea nitrogen [BUN] ≥1.5 × upper limit of normal (ULN) or estimated glomerular filtration rate [GFR] <45 mL/min/1.73 m^2 and corroborating medical history and physical examination). See the Study Laboratory Manual for details of GFR calculation.

30. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

31. Current hepatitis C infection (defined as positive hepatitis C virus [HCV] antibody and detectable HCV ribonucleic acid [RNA]). Subjects with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study (United States Centers for Disease Control and Prevention).

32. History of or positive test result at Screening for human immunodeficiency virus (HIV). The requirement for testing at screening may be omitted if it is not permitted by local regulations.

33. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months of screening.

34. Use of tobacco- or nicotine-containing products in excess of the equivalent of 40 cigarettes per day.

35. Triplicate 12-lead ECGs demonstrating average QTcF >450 msec for men and >470 msec for women or an average QRS interval >120 msec at the Screening or Baseline /Day 1 Visit.

36. History of risk factors of QT prolongation or torsades de pointes (e.g., heart disease, congestive heart failure, hypokalemia, hypomagnesaemia, congenital long QT syndrome, myocardial ischemia, or infarction), congenital deafness, and family history of sudden death before age 60 as determined by the Investigator.

37. Suicide attempt within the last 2 years. Subjects who, in the Investigator's judgment, pose a significant suicide risk, or who have suicidal ideation associated with actual intent and a method or plan in the past 6 months (i.e., "Yes" answers on items 4 or 5 of the C-SSRS) will be excluded from the study.

38. Evidence or history of current clinically significant medical or psychiatric illness that could preclude the subject from completing all aspects of this clinical trial, as determined by the Investigator in discussion with the Sponsor.

Subject eligibility should be reviewed and documented in the source documents by an appropriately qualified member of the Investigator's study team before subjects are reviewed by the Sponsor for confirmation of eligibility.

8.3. Lifestyle Guidelines

The following lifestyle guidelines are provided:

8.3.1. Meals and Diet

There are no meal or dietary restrictions. Study treatment can be taken with or without food; however, subjects should remain fasted for 2 hours before and after taking the dose of study treatment associated with [redacted]. Time and date of food consumption should be recorded in the source documentation if the study treatment is taken at the clinical sites. All [redacted] are dependent on individual subject availability and it will not be considered a protocol deviation if the subject is not able to comply with recommended [redacted].

8.3.2. Alcohol, Caffeine, and Tobacco

Because the potential for interactions between the study treatment and alcohol have not yet been evaluated, subjects are prohibited from consuming alcohol for the duration of the study. Urine

drug and alcohol testing is performed at Screening and other timepoints during the study (see Table 4). In addition, subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the Investigator. Subjects should adhere to their usual regime of caffeine and tobacco (to maximum of 40 cigarettes or equivalent per day) as appropriate.

8.3.3. Activity

Subjects should avoid driving or operating potentially hazardous machinery until it is clear they are not experiencing adverse treatment effects that might interfere with their ability to drive or operate potentially hazardous machinery.

Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

8.3.4. Contraception

The Investigator or designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see Section 15.5) and will instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The Investigator or designee will discuss with the subject the need for using highly effective contraception consistently and correctly, per the Schedule of Activities tables (Section 5) and will document the conversation in the subject's record.

Contraception and pregnancy testing requirements must also be consistent with the contraception/pregnancy testing guidance for any background antipsychotic medication a subject is taking (as stated within their approved product labels). In addition, the Investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

9. SCREENING AND RANDOMIZATION

9.1. Screening

Subjects must provide informed consent before any screening tests are performed (see Section 17.3). Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

The interactive response technology (IRT) system will provide the subject identification number at the end of the IRT subject screening transaction. This unique subject identification number is assigned sequentially to each subject who has signed the informed consent form (ICF). This identifying number will be retained throughout the duration of the study participation.

Screen failures are defined as subjects who sign the ICF but are not subsequently randomized. If a subject is considered a screen failure, this must be registered in the IRT; the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Individuals who do not meet the criteria for participation in this study (i.e., a screen failure) may be rescreened at the discretion of the Investigator and approval by the Sponsor (see Section 9.3).

Site screening procedures need to be completed within 3 out of 5 consecutive working days from the beginning of screening procedures to enable Sponsor Eligibility Verification. At screening, the informant interview must be conducted in person; however, the interview does not need to be conducted at the study site. The informant interview does not have to occur on the same day as the subject interview; however, the informant interview should, wherever possible, be completed within 3 days of the relevant subject screening procedures (e.g., SCI-PANSS, SCoRS). The Screening Visit should be scheduled as close as possible to when the informed consent is signed to allow maximum time for the subject eligibility process.

In order to prevent subject fatigue during assessments, it is acceptable for subjects to take a short break between assessments. Screening procedures may be completed over a maximum of 3 out of 5 consecutive days for feasibility and subject comfort.

9.1.1. Screening Assessments

For a list of all screening assessments and procedures, see Table 3. Assessments that are conducted at screening and at other timepoints during the study are described in the appropriate sections, e.g., Clinical Efficacy Assessments (Section 13.1), Clinical Safety Assessments (Section 14.1). Some screening assessments may be recorded (see Study Reference Manual for further details). Assessments that are performed only at screening are described below.

9.1.1.1. Validated Reading Test

A validated reading test can provide an intelligence quotient (IQ) estimate. A standard score of ≥70 on such an assessment is required for participation in the study.

9.1.1.2. Mini-International Neuropsychiatric Interview for Psychotic Disorders 7.0.2

The MINI 7.0.2 for Psychotic Disorders is a short, structured diagnostic interview that was developed for DSM-5 and International Statistical Classification of Mental and Behavioral Disorders, 10th revision (ICD-10) psychiatric disorders and has been validated against the Structured Clinical Interview for DSM (SCID) diagnoses. It will be used to assess diagnosis of schizophrenia for study inclusion and will also be used to assess for excluded psychiatric conditions outlined in the study exclusion criteria.

9.1.1.3. Independent Telemedicine Interview

Following the initial Screening Visit, a telemedicine interview with an independent research interviewer will be performed to confirm that each subject meets criteria for diagnosis of schizophrenia. This assessment will be based on the Massachusetts General Hospital (MGH) SAFER criteria (State versus trait, Accessibility, Face validity, Ecological validity, Rule of 3 p's [pervasive, persistent, and pathological]) [Desseilles 2013]. The subject's illness must be deemed "valid" according to SAFER criteria in order to participate in the study.

9.2. Placebo Lead-In

This study will employ a medication adherence monitoring platform for all subjects in the study. The platform uses an application for smart phones to confirm medication ingestion in addition to built-in reminders and a communication system that allows real-time intervention in case of drug interruptions. See the Study Reference Manual for further description and detailed instructions on training for and use of the monitoring platform.

As part of the screening and eligibility process, in order to assess overall compliance with the planned dosing regimen and to assess the subject's ability to operate the monitoring platform, a 7-day placebo lead-in evaluation will take place after the initial screening is completed (see Table 3). A Placebo Lead-In Visit will be scheduled to start the 7-day test, at which time the subject will be instructed on the use of the monitoring platform. A 7-day supply of placebo will be issued to the subject with instructions for dosing over the test period, which must be completed no earlier than 3 days prior to the Baseline/Day 1 Visit.

At the Baseline/Day 1 Visit, confirmation of compliance will be documented. Compliance during the lead-in period is defined as at least 80% of the medication ingested within the allowable time frames and recorded using the monitoring platform.

9.3. Subject Rescreening

A subject may be considered for rescreening in this study. As a general rule, depending on the timing of rescreening relative to the original screening procedures, the battery of screening safety assessments to be repeated will depend on whether these tests were already beyond the 35 days from the original screening date. Subjects who are being considered for rescreening by the Investigator must be discussed with the Sponsor to identify the subject-specific rescreening safety assessments required. Rescreening may be permitted in the case of a temporary condition that is expected to resolve.

In the event that repeat safety screening assessments are needed during the screening phase (e.g., for misplaced ECG leads or hemolyzed blood sample) that lead to >35 days in the screening period (e.g., due to scheduling difficulties), this must be discussed with the sponsor to determine subject eligibility to continue in screening. In these scenarios, it will not be considered a protocol deviation if the Sponsor and Investigator, following a documented medical review, accept safety data that exceeds the 35-day screening window.

9.4. Subject Eligibility Review

The site will review and document eligibility for the subject in the source document. The site will review medical history, prior/concomitant medications, all laboratory tests, pregnancy tests, ECGs, and drug test results against inclusion/exclusion criteria.

9.5. Sponsor Screening Verification Process

The site will complete a pre-randomization form for subjects who meet the screening requirements. This form, along with other pertinent information as part of the eligibility assessment, will be submitted to the Sponsor's Medical Monitor for review and confirmation of certain inclusion/exclusion criteria prior to randomization. **Randomization may not proceed without Sponsor approval.**

9.6. Randomization

Subjects will be randomized after all screening assessments and placebo lead-in have been completed and after the Investigator and the Sponsor have verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Randomization will be performed using IRT. Randomization will be stratified by region. Subjects will be randomized in a 1:1:1 ratio to receive one of the following:

- BIIB104 0.15 mg
- BIIB104 0.5 mg
- placebo

Refer to the Study Reference Manual for additional details on randomization.

9.7. Blinding Procedures

All study staff will be blinded to the subject treatment assignments. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except designated Biogen personnel.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject must permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately, and the pregnancy must be reported according to the instructions in Section 15.4.1.
- Any seizure event. If a seizure event is suspected, the subject must discontinue study treatment and be referred to a neurologist for appropriate follow-up (see Section 7.3). An effort should be made to collect a [redacted] as soon as possible after the event.
- The subject withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE requiring continued treatment that meets exclusionary criteria.
- The subject has confirmed ALT or AST >5 ×ULN, or confirmed ALT or AST >3 × ULN and bilirubin >2 × ULN.
- Depending on the specifics of the subject's C-SSRS as assessed by the Investigator, subjects must have their suicidality managed appropriately by clinicians and must discontinue from the treatment.
- At the discretion of the Investigator, for medical reasons.
- At the discretion of the Investigator or the Sponsor, for noncompliance with the terms of the protocol.
- The primary reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

All subjects who discontinue study treatment prematurely will be asked to remain in the study and continue all protocol-specified visits and procedures. At a minimum, these visits should include assessment of AEs/SAEs and concomitant medications and key clinical assessments. Subjects who discontinue study treatment prematurely will also be asked to return to the study site for an SFU Visit 14 days after receiving the last dose of study treatment.

10.2. Subject Early Termination/Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

Subjects must be withdrawn from the study for any one of the following reasons:

- At the discretion of the Investigator for medical reasons.
- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

The primary reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects who withdraw from the study will not be replaced.

10.3. Lost to Follow-Up

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject (e.g., the subject's informant). Lost to follow-up is defined as the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return all unused study treatment, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

Randomized, blinded study treatment will be self-administered orally by the subject BID for the duration of the treatment phase. Duration of treatment will be approximately 85 days, for a total of approximately 169 doses (assuming only 1 dose on Day 85).

Subjects will be randomized in a 1:1:1 ratio to receive one of the following treatment regimens:

- BIIB104 0.15 mg BID orally for 12 weeks
- BIIB104 0.5 mg BID orally for 12 weeks
- Placebo BID orally for 12 weeks

Subjects will take 1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart. Subjects are to swallow the capsules whole and not manipulate or chew the capsules prior to swallowing. Study site personnel will supervise subjects taking the first dose on Day 1 at the investigative site. At subsequent visits, study treatment will be dispensed after all study procedures have been completed for the respective visit or as directed on [redacted].

11.2. Modification of Dose and/or Treatment Schedule

If a subject misses a scheduled morning dose, subjects should be instructed that the dose should be taken as soon as possible, but no later than 6 hours after the scheduled time of dosing. If it is more than 6 hours after the scheduled time of dosing, the subject should be instructed to skip that dose and resume dosing at the next regularly scheduled time.

11.3. Compliance

Dosing compliance is documented in the drug accountability logs, electronic Case Report Form (eCRF) and by the medication compliance platform. Study treatment will be dispensed in blister cards. Subjects should make every attempt to self-administer the treatment daily as instructed. The subject will bring the blister cards back to the clinic at each visit. At each visit, a capsule count will be done by the research staff, and the subject will be questioned about any missed or extra doses taken. **Based on blister card review and/or capsule count, any subject who is noted not to have taken at least 80% or has taken more than 100% of required doses at any scheduled visit during the study will be considered out of compliance. See Study Reference Manual for additional information.**

If a subject is out of compliance, the Investigator will need to discuss the subject's continuation in the study with the Sponsor's Medical Monitor. Based upon the assessment of the Investigator and Sponsor's Medical Monitor, an out-of-compliance subject may be withdrawn from the study. All dispensed investigational product blister cards will be kept available for routine study checks by the Sponsor's Study Monitor. The time of subject dosing will be reviewed by the Study Monitor from the medication compliance application.

A smart phone-based medication compliance application will be used to assist the subject with medication compliance. See Section 9.2 for a brief description of the application. See the Study Reference Manual for further description and detailed instructions on the training and use of the monitoring platform.

11.4. Concomitant Therapy and Procedures

11.4.1. Concomitant Therapy

Note that discontinuation of prohibited concomitant treatments for the sole purpose of enabling the subject to qualify for participation in Study 263CS201 should only occur after the subject and their informant have signed their respective Informed Consent Documents.

Concomitant therapy guidelines will be provided in the Study Reference Manual.

- As defined in the inclusion criteria, subjects must be receiving ongoing maintenance atypical antipsychotic therapy other than clozapine (oral or depot) on a stable treatment regimen for ≥8 weeks prior to Baseline/Day 1, including concomitant psychiatric medications. Doses of background atypical antipsychotics should be within the recommended dose range listed in the approved product labeling of the country where the study is being conducted. Doses exceeding the recommended dose range are not permitted and doses below the recommended dose range should be discussed with the Sponsor's Medical Monitor. Subjects should be taking no more than 2 background antipsychotics.
- Treatment regimen stability is defined as maintaining the same dosage of treatment except for minor adjustments (≤25%) to manage medication-specific tolerability issues. Note that hypnotics are an exception to this stability requirement; prohibited hypnotics may be substituted with allowed hypnotics administered as described below.
- Stable concomitant treatment with a second atypical antipsychotic at doses that do not exceed the range listed in the approved product labeling of the country where the study is being conducted is permissible if used for a targeted symptom (e.g., insomnia) or an adverse effect from the primary maintenance antipsychotic treatment, but not if it is used for refractory psychotic symptoms. Subjects should be taking no more than 2 background antipsychotics.
- Compliance with background antipsychotic medication regimen will be monitored during the study.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Prohibited treatments must be washed out for a minimum of 5 half-lives of the treatment prior to randomization. Allowable exceptions to this rule include the following:

- The as-needed treatment of anxiety or agitation with up to 2 mg/day lorazepam (or the equivalent dose of another short-acting benzodiazepine) with the following restrictions:
    - Not used within 8 hours of neurological assessments (e.g., neurological examination, SARA) or within 12 hours of scheduled efficacy assessments (e.g., MCCB, SCI-PANSS, UPSA-Bi, SCoRS).
- The as-needed treatment of insomnia with nonbenzodiazepine hypnotics (e.g., zolpidem up to 10 mg/day, zaleplon up to 20 mg/day, eszopiclone up to 3 mg/day) are permitted within their respective recommended dose ranges with the following restriction:
    - Not to be used within 12 hours of scheduled efficacy assessments.
- Minor adjustment (≤25% of the baseline dose) of the dosage of background atypical antipsychotics or psychiatric medications for tolerability. This option should be used only if required to support a subject's continued participation in the study. All efforts should be made to maintain background pharmacotherapy at consistent doses throughout the treatment phase of the study. Recognizing that physicians outside of the study may be managing the subject's background atypical antipsychotic and other psychiatric medications, changes in background medication dosing that exceed this limit should be discussed with the Sponsor's Medical Monitor to determine subject disposition.
- As-needed treatment with any other nonprohibited treatment with potential psychotropic effects (e.g., centrally acting antihistamines) should not occur within 12 hours of scheduled efficacy assessments.
- Acetaminophen and nonsteroidal anti-inflammatory medications may be used intermittently throughout the study.
- The chronic use of certain medications (some hormones, antihypertensives, diuretics, and oral hypoglycemics) is allowed if the subject was prescribed these treatments at least 8 weeks prior to study entry, the treated condition is stable, and the dosage is stabilized prior to the first dose of study treatment. Potential exceptions to the 8-week requirement may be allowed on an individual basis in consultation with the Sponsor's Medical Monitor to determine whether it is appropriate to include the subject in the study. If changes are required to chronic treatments during study participation, these should be discussed with the Sponsor's Medical Monitor to determine appropriateness for the subject's continued participation.
- Nicotine therapy (including patches), varenicline, or similar therapeutic agents to support smoking cessation are permitted if they have been introduced as treatment prior to the Screening Visit.

The following drugs, classes of drugs, foods, and other nonpharmacological treatments are prohibited as concomitant treatments after the Screening Visit (see the Study Reference Manual for additional information):

- Medications that may lower seizure threshold, including but not limited to aminophylline, theophylline, chlorpromazine, clozapine, cyclosporine, pethidine, bupropion, clomipramine, maprotiline, and amantadine. The Investigator should discuss the use of any concomitant treatment associated with lowering seizure threshold with the Sponsor's Medical Monitor prior to randomizing a subject.
- Medications or foods/food products that are strong inhibitors of CYP3A4, including but not limited to: grapefruit juice, boceprevir, cobicistat, conivaptan, danoprevir, elvitegravir, indinavir, ketoconazole (topical use is permitted), lopinavir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, tipranavir, troleandomycin, voriconazole.
- Medications or supplements that significantly induce CYP3A4, including but not limited to: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort.
- Anorectics and stimulants
- Opioids
- Treatments with anticholinergic activity, including but not limited to hydroxyzine, hyoscyamine, methscopolamine, scopolamine, amitriptyline, imipramine, doxepin, diphenhydramine, atropine, cyclobenzaprine hydrochloride, orphenadrine citrate, benztropine mesylate, and trihexyphenidyl. The Investigator should discuss the use of any concomitant treatment associated with anticholinergics with the study Medical Monitor prior to randomizing a subject. (Note: Treatment with anticholinergics for extrapyramidal motor symptoms is permitted at no more than the equivalent of 1 mg benztropine BID.)
- Typical antipsychotic treatments, including but not limited to prochlorperazine, haloperidol, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, trifluoperazine, chlorpromazine, and perphenazine. The Investigator should discuss the use of any concomitant treatment associated with typical antipsychotic treatments with the study Medical Monitor prior to randomizing a subject.
- Vitamin K antagonists, including but not limited to warfarin.
- Antiepileptics, including but not limited to valproate, carbamazepine, phenytoin, oxcarbazepine, and phenobarbital. The Investigator should discuss the use of any concomitant antiepileptic treatment with the Sponsor's Medical Monitor prior to randomizing a subject. Some antiepileptics are permitted if not being used as antiseizure treatments; these include but are not limited to pregabalin, gabapentin, and lamotrigine.
- Anti-emetics with dopamine antagonist action (e.g., metaclopramide, prochlorperazine).
- Herbal supplements (must be discontinued at least 28 days before the first dose of trial treatment)
- Lithium
- Cognitive remediation therapy and electroconvulsive therapy

Note that treatments taken within 28 days before the first dose of study treatment will be documented as a prior treatment. Treatments taken after the first dose of study treatment will be documented as concomitant treatments.

11.4.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and last study visit.

All subjects will be asked about concomitant procedures at each clinic visit, and all procedures reported by subjects will be documented.

12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study.

12.1. BIIB104 Study Treatment

BIIB104 and its matched placebo will be provided as capsules (Size 1) for oral administration. The BIIB104 0.15 mg and 0.5 mg capsules and their matched placebos will be supplied in separate blister cards and labeled in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site staff. Study treatment should not be used after the expiration, expiry, or use-by date.

12.1.1. BIIB104 Preparation and Dispensing

The study treatment will be dispensed using the IRT drug management system. A qualified staff member will dispense the treatment via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The subject and informant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

12.1.2. BIIB104 Storage

The Investigator, or an approved representative (e.g., pharmacist) will ensure that all study treatments are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Study treatment should be stored in its original container and in accordance with the label. The label is the primary source of information for storage conditions and will supersede any other document references to storage conditions.

Site systems must at a minimum be capable of measuring and documenting (e.g., via a log) daily minimum and maximum temperatures for all site storage locations (including frozen, refrigerated, and/or room temperature products, as applicable). This should be captured from the time of receipt of study treatment throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. As

applicable, the operation of the temperature monitoring device and storage unit (e.g., refrigerator) should be regularly inspected to ensure it is maintained in working order.

Any deviations from the product label storage conditions should be documented upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once a deviation is identified, the study treatment must be quarantined and not used until the Sponsor provides documentation of permission to resume use. It will not be considered a protocol deviation if the Sponsor approves the use of the study treatment after the temperature deviation. Use of the treatment in question prior to Sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for any deviation will be provided separately to the site in the Study Reference Manual.

Site staff will instruct subjects on the proper storage requirements for take-home study treatment.

12.1.3. BIIB104 Handling and Disposal

The Investigator must return all used and unused packages of BIIB104 study treatment name as instructed by the Sponsor unless approved for onsite destruction.

If any BIIB104 supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BIIB104 Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all blister cards, both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BIIB104 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

Subjects should make every effort to return all unused study treatment and all blister cards to the site at each visit. Unused study treatment and unused or used study treatment materials must be kept in a secure location for final accountability and reconciliation.

12.2. Placebo

Subjects will receive a matched placebo for oral administration using a dosing regimen identical to that of the active BIIB104 treatment groups for the study treatment periods as well as for the placebo lead-in assessment.

Excipients for the manufacturing of the placebo drug product are the same excipients used in the active drug product strengths, minus the BIIB104 active ingredient. The placebo is encapsulated in a #1 LiCap hard gelatin, white opaque capsule.

Placebo is to be stored under the same conditions as BIIB104.

13. EFFICACY AND PHARMACOKINETIC ASSESSMENTS

See the Schedules of Activities in Section 5 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the study site to have the evaluations repeated.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BIIB104. All assessments will be administered as specified in the Schedules of Activities for this protocol. Some assessments may be recorded (SCI-PANSS and SCoRS – audio recording of subject, optional audio recording of informant; MCCB – video recording of rater) in order to allow for central review for standardization of test administration, where allowable by country and/or local authorities.

13.1.1. MATRICS Consensus Cognitive Battery

The MCCB is a cognitive battery that assesses 7 domains recommended by the MATRICS initiative (i.e., Working Memory, Verbal Learning, Speed of Processing, Attention/Vigilance, Visual Learning, Social Cognition, and Reasoning and Problem Solving). Scores for the individual tests will be calculated according to the developer's recommended scoring algorithms. The MCCB is administered via laptop computer and paper-and-pencil assessments. The subjects will be administered the test in a quiet, distraction-free environment.

[redacted]

[redacted]

13.1.5. Structured Clinical Interview for Positive and Negative Syndrome Scale

The SCI-PANSS includes 3 scales and 30 items: 7 items that make up the Positive Scale (e.g., delusions, conceptual disorganization, hallucinatory behavior); 7 items that make up the Negative Scale (e.g., blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal); and 16 items that make up the General Psychopathology Scale (e.g., somatic concern, anxiety, guilt feelings, mannerisms and posturing, motor retardation, uncooperativeness, disorientation, poor impulse control, preoccupation). Individual items are scored with values ranging from 1 to 7. SCI-PANSS ratings are made after the completion of a semi-structured interview, using additional reports of daily function from caregivers and family members and a review of available clinical material.

13.1.6. University of California, San Diego, Performance-Based Skills Assessment – Brief, international version

The UPSA-Bi, an abbreviated version of the UPSA-Validation of Intermediate Measures, is a measure of functional capacity and assesses skills used in community tasks. This assessment measures 2 general skills that were previously identified as essential to functioning in the community: financial skills and communication skills. The assessment involves role-play tasks that are administered as simulations of events that the person may encounter in the community.

13.1.7. Schizophrenia Cognition Rating Scale

The SCoRS is an interview-based assessment of cognition that involves interviews with subjects and informants. The SCoRS includes 20 items designed to specifically assess aspects of cognitive functioning found in each of the seven MCCB cognitive domains, including the following:

- Memory: 4 items
- Learning: 2 items
- Attention: 3 items
- Working Memory: 2 items
- Problem Solving: 3 items
- Processing/Motor speed: 2 items
- Social cognition: 3 items
- Language: 1 item

13.1.8. Clinical Global Impression of Severity

The CGI-S consists of a single 7-point rating score of illness severity. Raters select one response based on the following question: "Considering your total clinical experience with this particular population, how mentally ill is your patient at this time?" Scores are as follows: 1, Normal, not ill at all; 2, Borderline mentally ill; 3, Mildly ill; 4, Moderately ill; 5, Markedly ill; 6, Severely ill; or 7, Among the most severely ill subjects.

13.1.9. Clinical Global Impression of Improvement

The CGI-I consists of a single 7-point rating score total improvement, regardless of whether or not the change is due entirely to drug treatment. Raters select one response based on the following question: "Compared to your patient's condition at the beginning of treatment, how much has your patient changed?" Scores are as follows: 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse. For the CGI-I scale, the subject's condition at the Baseline/Day 1 Visit will be the criterion for judging improvement at subsequent visits. For the CGI-I, the CGI-S at baseline will be the criterion for judging improvement at subsequent visits.

[redacted]

[redacted]

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

See Section 5 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB104.

14.1.1. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

The full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The brief physical examination will be focused on general appearance and respiratory and cardiovascular systems, as well as on subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

14.1.2. Neurological Examinations

The full neurological examination includes observation for cerebellar (intention) tremor and noncerebellar (e.g., resting or positional) tremor, nose-finger, heel-shin, Romberg, tandem walk, normal walk/gait, positional nystagmus, gaze-evoked nystagmus, reflexes, muscle strength, cranial nerves, and sensory function of the upper and lower extremities. The neurological examination will be performed by a physician or the equivalent.

The brief neurological examination will include an assessment of motor and sensory function, cranial nerves, reflexes, noncerebellar tremors (e.g., resting or positional), and cerebellar function. The assessment of cerebellar function will be complemented by the SARA. The brief neurological examinations will be conducted by a physician or the equivalent.

14.1.3. Scale for the Assessment and Rating of Ataxia

The SARA will be conducted by a physician or the equivalent with experience in neurological assessment.

The SARA is a clinical scale that is based on a semiquantitative assessment of cerebellar ataxia on an impairment level and will complement the brief neurological examination. The SARA has 8 items that are related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test [Schmitz-Hübsch 2006].

14.1.4. Columbia-Suicide Severity Rating Scale

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior. Versions are available for Screening, Baseline, and follow-up visits.

The C-SSRS should be collected at the times specified in Schedules of Activities (Section 5) by an appropriately trained site staff member. The C-SSRS can also be administered at any time in the study at the discretion of the Investigator based on any reasonable concern.

The following subjects will be excluded from study participation:

- Subjects who have attempted suicide within the last 2 years.
- Subjects who, in the Investigator's judgment, pose a significant suicide risk.
- Subjects who have suicidal ideation associated with actual intent and a method or plan in the past 6 months (i.e., "Yes" answers on item 4 or 5 of the C-SSRS).

At each suicidality assessment following the Screening Visit, subjects believed to have significant suicidal ideation with actual plan and intent or with suicidal behavior must be evaluated by a licensed and qualified mental health professional (MHP) [e.g., a psychiatrist or licensed PhD level clinical psychologist] skilled in the evaluation of suicidality by virtue of training or experience who will determine whether it is safe for the subject to continue in the trial. Specific criteria that indicate a need for such an assessment include the following:

- Suicidal ideation associated with actual plan and/or intent since last visit; (Yes answer to C-SSRS question 4 [some intent to act without specific plan] or 5 [specific plan and intent]).
- In the Investigator's judgment, a risk assessment or exclusion is warranted.

Suicidality AEs or other clinical observations, based on the judgment of the Investigator and/or clinician/MHP, may also trigger a risk assessment and a narrative using information from the C-SSRS, and other available information including psychiatric/medical history.

Subjects who respond "Yes" to item 4 or 5 or to any behavioral question of the C-SSRS at any time after the baseline visit will be assessed by the clinician/MHP to determine whether an AE has occurred and whether it is safe for the subject to continue in the trial.

Subjects who respond "Yes" to item 4 or 5 or to any behavioral question of the C-SSRS on more than one occasion during the study must have their suicidality managed appropriately by the Investigator together with clinician/MHP (or the Investigator alone if they are a qualified mental health professional). Depending on the specific circumstances as assessed by the Investigator and/or clinician/MHP, the subject may be withdrawn from the study.

14.1.5. Blood Pressure and Pulse Rate

Supine blood pressure will be measured with the subject's arm (preferably the dominant arm) supported at the level of the heart and recorded to the nearest measurement (mmHg) after approximately 5 minutes of rest. The same arm should be used throughout the study.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring blood pressure and pulse rate is acceptable; when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

14.1.6. Electrocardiogram

Triplicate and single ECGs will be collected as specified in the Schedules of Activities (Section 5). Samples obtained outside the proposed sampling timepoints specified in will not be captured as a protocol deviation, as long as the exact time of the assessment is noted on the source document and data collection tool (e.g., CRF).

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dosing on Day 1 will serve the subject's baseline QTc value. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure, and pulse rate.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected (approximately 2 to 4 minutes apart) to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥45 msec above the baseline) or is ≥500 msec, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values are >500 msec (or ≥45 msec above the baseline) for more than 4 hours (or sooner at the discretion of the Investigator), or if QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to <500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the Investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

14.2. Laboratory Safety Assessments

The following parameters will be analyzed from samples collected from subjects at the times specified in Section 5. Samples will be analyzed using Good Laboratory Practice-validated assays.

- Complete blood count including: red blood cell count, white blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), hemoglobin, hematocrit, platelets, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

- Serum chemistry, including albumin, alkaline phosphatase, ALT, AST, BUN, bicarbonate, calcium, chloride, creatinine, creatine kinase, direct bilirubin, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides, total protein, and uric acid.

- Urinalysis, including urine protein, glucose, ketones, occult blood, and white blood cells by dipstick, with microscopic examination if indicated.

- Urine drug and alcohol testing (refer to the Study Reference Manual for complete list of drugs tested).

- At Screening Visit only: testing for human immunodeficiency virus (HIV) (to be performed based upon Investigator assessment of HIV risk factors; may be omitted if not permitted by local regulations); HbA1c, HBsAg, anti-HBc, anti-HBs, and hepatitis C antibody; and follicle-stimulating hormone (postmenopausal women only).

14.2.1. Pregnancy Testing

For female subjects of childbearing potential, a serum and urine pregnancy test with sensitivity of at least 25 mIU/mL, will be performed at times defined in Section 5. Urine pregnancy tests will be performed at the site; serum pregnancy tests will be performed at the central laboratory. A negative pregnancy result is required before the subject may receive the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and will be repeated at times defined in Section 5 to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRBs/ethics committees (ECs) or if required by local regulations.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. Qualitative point-of-service urine pregnancy tests will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the qualitative point-of-service urine test may not proceed further in the study until pregnancy is ruled out using

further diagnostic testing (e.g., a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive confirmed pregnancy, the subject will discontinue study treatment and be withdrawn from the study.

14.2.2. Antipsychotic Medication Monitoring

Background antipsychotic medication blood levels will be tested at the times specified in Section 5 and analyzed using a validated analytical method at a College of American Pathologists/Clinical Laboratory Improvement Act certified laboratory. For all visits, the time of the sample collection will be documented as well as the time, date, and dosage of the 2 most recent doses of primary background antipsychotic medication prior to collection of the antipsychotic blood level sample. Details regarding the collection, processing, storage, and shipping of the blood samples will be in the laboratory manual that is provided to the investigative site prior to the initiation of the study.

14.3. Japan-Specific Safety Assessment on Day 8

All subjects enrolled at sites in Japan will undergo a review of their safety data following the Day 8 Visit. For this review, the Investigator will assess the available blinded safety data for the subject for the initial 8 days of dosing (Days 1 through 8), including, but not limited to: all available AEs, SAEs, vital signs, ECGs, and clinical assessments. The Investigator will communicate any abnormal findings to the Biogen Medical Director and Medical Safety Officer (refer to the Study Reference Manual for communication process). The Biogen Medical Director and Medical Safety Officer will then decide whether it is safe for a subject to continue in the study by confirming, at a minimum, that the discontinuation of study treatment rules (see Section 10.1) and the study stopping rules criteria (see Section 7.3) have not been met and that there are no additional safety concerns. If additional clinically relevant data become available (e.g., laboratory results), the Investigator will inform the Biogen Medical Director and Medical Safety Officer. This review of safety data will be documented.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject and/or main caregiver must be given the names and telephone numbers of site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value, vital sign result, and/or ECG result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the subject to receive specific corrective therapy
- The result is considered by the Investigator to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and subject's final clinic visit (including the SFU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the

Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the CRF, as applicable.

15.3.2. Adverse Events of Special Interest

An AE of special interest is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting are required.

For this protocol, any event of seizure should be considered as medically significant and be reported as an SAE.

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the subject's final clinic visit (including the SFU Visit) is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen within 24 hours as described in Section 15.3.4. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed for all SAEs until the subject's final clinic visit (including the SFU Visit). Thereafter, the event should be reported to Biogen only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the Sponsor within 24 hours of the site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

A report ***must be submitted*** to the Sponsor regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, refer to the Study Reference Manual's Official Study Contact List for complete contact information.

15.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Appropriate Sponsor personnel will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for at least 30 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject or the partner of a male subject by transmitting the appropriate form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Manual's Official Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and transmitted to the Sponsor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and transmitted to the Sponsor. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the Sponsor's Medical Monitor. Refer to the Study Reference Manual for contact information.

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents.

The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact the Sponsor to discuss such situations but such a discussion should not delay management of the medical emergency.

15.5. Contraception Requirements

All women of childbearing potential and all men must practice highly effective contraception during the study and for at least 30 days after their last dose of study treatment. In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 3 months after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria listed below are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level >40 mIU/mL
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted hormonal methods of contraception that contain progestogen alone associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- The use of condoms with spermicide.
- Sex with a woman who uses the methods described for females if she is of childbearing potential.
- Male surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female subjects and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any subjects, the Medical Monitor is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Efficacy

16.1.1. Analysis Population

Analysis of efficacy endpoints will be based on the intent-to-treat (ITT) population.

The ITT population is defined as all randomized subjects who received at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment to which they were randomized. Analysis of other nonsafety endpoints (e.g., demographics) will also be based on the ITT population, unless otherwise specified in the statistical analysis plan (SAP). Other analysis populations will be defined in the SAP.

16.1.2. Methods of Analysis

Continuous variables will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by timepoint and treatment group. Point estimates and 90% CIs will be provided where applicable.

16.1.2.1. Analysis of the Primary Endpoint

The primary endpoint is the change of MCCB Working Memory Domain score from baseline to Week 12. An MMRM model will be used as the primary analysis to analyze change from baseline in Working Memory Domain score using fixed effects of treatment, visit, treatment by visit interaction, baseline Working Memory Domain score, baseline Working Memory Domain score by visit interaction, and region.

In the analysis of the primary endpoint, missing data will be assumed to be missing at random (MAR). An unstructured variance-covariance structure will be used to model the within patient measurements variability. If this analysis fails to converge, other structures will be tested such as heterogeneous autoregressive, heterogeneous compound symmetry, or heterogeneous Toeplitz. The variance-covariance structure that results in the smallest Akaike information criterion will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Sensitivity analyses will be carried out to assess the robustness of primary analysis to deviation from the MAR assumption. Details of sensitivity analyses and assumptions for different missing patterns will be described in the SAP.

16.1.2.2. Analysis of the Secondary Endpoints

The secondary endpoints are defined in Table 6. The population for the analysis will be subjects in the ITT population with a baseline and at least 1 postbaseline value. For all continuous endpoints, an MMRM model will be used to analyze change from baseline to Week 12 visit using the fixed effects of treatment, visit, treatment-by-visit interaction, baseline, baseline-by-visit interaction, and region. Sensitivity analyses based on different missing mechanism will also be performed (imputation methods are defined in the SAP).

[redacted]

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment (including active treatment and placebo).

16.4.2. Methods of Analysis

All AEs, laboratory data, vital signs, SARA, and C-SSRS will be evaluated for safety.

16.4.2.1. Adverse Events

AEs will be coded using the available, current version of the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) will be defined as any AE that started or worsened in severity after initial dose of study treatment through the follow-up phase; hereafter, TEAEs will be referred to simply as AEs. AEs will be grouped by system organ class, preferred term, and overall, and then summarized. The incidence, severity, and relationship to study treatment will be summarized, separately for all AEs, treatment-related AEs, and SAEs.

16.4.2.2. Clinical Laboratory Results

Clinical laboratory evaluations will include hematology, blood chemistry, and urinalysis. Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum postbaseline value and the shift from baseline to the minimum postbaseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant postbaseline abnormalities will be presented by treatment group.

16.4.2.4. C-SSRS

C-SSRS data will be summarized by each treatment group.

16.5. Interim Analyses

An interim analysis for futility of the primary endpoint may be performed after approximately 50% of the subjects have had an opportunity to complete the Week 12 Visit. No test for superiority will be performed at the interim analysis; therefore, no alpha spending will be incurred.

In order to maintain the treatment blind, a separate unblinded team will be formed to perform the interim analysis. All other study personnel who are involved in the conduct of the study will remain blinded. Details will be specified in the unblinding plan.

The details of the futility criteria are included in the SAP.

16.6. Sample Size Considerations

Fifty-one subjects per treatment group will have approximately 80% power to detect a true mean difference of 3.5 in change from baseline MCCB Working Memory Domain score to Week 12 between the treatment and placebo groups. With the assumed drop-out rate of 30%, 73 subjects are required from each group to maintain the 80% power. This power calculation is based on a 2-sided *t*-test assuming equal variance with a final significance level of 0.1, and an SD of 7. The statistical software EAST 6.3® is used for sample size calculation. The sample size may be re-estimated based on blinded data review and evolving development of this study.

17. ETHICAL REQUIREMENTS

The Sponsor, all vendors and CROs, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator is responsible for endorsing all data on completed CRFs electronically, prior to any interim lock or database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor will submit documents will submit documents on behalf of the study sites worldwide in compliance with local regulations.

If the Investigator makes any changes to the ICF, the Sponsor must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and the Sponsor.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results.

Subjects will also be informed that audio or video recordings may be made of some clinical assessments in order to allow for central review for standardization of test administration, where allowable by country and/or local authorities.

Where allowed by local, regional, and national regulatory authorities and ethics committees (and Investigator discretion at Japan study sites), subjects will be offered an option for residual [redacted] to understand the biology of other diseases and traits of interest to Biogen other than schizophrenia or BIIB104 and/or to develop diagnostic and analytical tests. [redacted]

A copy of the signed and dated ICF must be given to the subject. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

The subject's caregiver/informant must also provide written informed consent to participate in the study. The original forms will be managed and archived in the same manner as the subjects' ICFs, as described above.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During Screening, subjects' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). Race and ethnicity data will be used to describe the demographic profile of the study population and to evaluate the balance of demographic characteristics across the randomized treatment groups. These data may also be used in the analysis of the safety and/or [redacted] of the study

treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

Video recordings will be made and may be transmitted in order to confirm dosing compliance.

Audio or video recordings may be made of some clinical assessments in order to allow for central review for standardization of test administration, where allowable by country and/or local authorities. All audio and video recordings of clinical assessments will be sent to each respective site per subject at the end of the study, kept by the vendor 1 year from last subject's last visit, then subsequently destroyed, and not sent to Biogen for archiving purposes.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

The Sponsor will register the study and post-study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by the Sponsor. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all CRF data prior to any interim or final database lock.

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitors will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and the Sponsor.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

The Sponsor will be responsible for all administrative aspects of this study including but not limited to study initiation, monitoring, management of AEs, and data management.

The Sponsor will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study, including but not limited to study initiation, monitoring, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool configured by the Sponsor and hosted by the electronic data capture vendor.

Clinical Outcome Assessments (COAs) will be administered electronically and/or via paper depending on the scale selected, as outlined in the Study Reference Manual. If data are entered electronically, the subject, caregiver/informant, rater, and/or site staff will enter the values into the electronic tablet per the tablet scale instructions. If entered via paper administration, the subject, caregiver/informant, rater, and/or site staff will enter the values in the provided paper form per the instructions in the Study Reference Manual. Site staff will monitor the data via a secure Web-based portal developed and supported by the electronic COA vendor.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to analyze all hematology, blood chemistry, and urine samples collected for this study. [redacted] will be analyzed at a laboratory selected by the Sponsor.

19.1.5. Central Facility for Other Assessments

An independent central vendor has been selected by the Sponsor to review and confirm diagnostic screening criteria.

A central facility has been selected by the Sponsor to read and interpret all ECG test results for this study.

19.2. Study Committees

19.2.1. Independent Data Monitoring Committee

An IDMC will monitor the progress of the study, review interim safety data, and oversee the safety of subjects participating in this study. The IDMC will meet periodically during the study to review AE listings and laboratory results for all enrolled subjects. In addition to the periodic meetings, the IDMC may meet on an ad hoc basis to address any issues of concern. An IDMC charter will be written and will contain additional details about the composition of the IDMC, as well as IDMC procedures and meetings.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition,

the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

The Sponsor will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by the Sponsor.

20. REFERENCES

Albus M, Hubmann W, Scherer J, et al. A prospective 2-year follow-up study of neurocognitive functioning in patients with first-episode schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2002;252(6):262-7.

Berry-Kravis E, Krause SE, Block SS, et al. Effect of CX516, an AMPA-modulating compound, on cognition and behavior in fragile X syndrome: a controlled trial. J Child Adolesc Psychopharmacol. 2006;16(5):525-40.

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993;361(6407):31-9.

Business Wire. Cortex 's AMPAKINE Compound, CX717, Achieves Primary Endpoints in Second Phase IIa Respiratory Depression Study in Germany. Published 2008 [Accessed 20 Jul 2018]. Available from: https://www.businesswire.com/news/home/20081006005597/en/Cortexs-AMPAKINE-Compound-CX717-Achieves-Primary-Endpoints

Chappell AS, Gonzales C, Williams J, et al. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. Neurology. 2007;68(13):1008-12.

Coles J, Oomman SK, Henne WM, et al. AMPA-induced dark cell degeneration is associated with activation of caspases in pyramidal neurons of the rat hippocampus. Neuroscience letters. 2008;436(3):294-9. Epub 2008/03/16.

Cortex. Cortex: Cortex To Present Data From Adult ADHD Study At AACAP Meeting 2006. 2006.

Desseilles M, Witte J, Chang TE, et al. Massachusetts General Hospital SAFER criteria for clinical trials and research. Harv Rev Psychiatry. 2013;21(5):269-74.

Eaton WW, Chen CY. Epidemiology. In: Leiberman JA, Stroup TS, Perkins DO, editors. Textbook of Schizophrenia. Washington DC: American Psychiatric Publishing; 2006. p 17-37.

Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. Am J Psychiatry. 2000;157(9):1416-22.

Garthwaite G, Garthwaite J. AMPA Neurotoxicity in Rat Cerebellar and Hippocampal Slices: Histological Evidence for Three Mechanisms. The European journal of neuroscience. 1991;3(8):715-728.

[redacted]

Goff DC, Lamberti JS, Leon AC, et al. A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. Neuropsychopharmacology. 2008;33(3):465-72. Epub 2007/05/09.

Goff DC, Leahy L, Berman I, et al. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. J Clin Psychopharmacol. 2001;21(5):484-7.

Grove SJ, Jamieson C, Maclean JK, et al. Positive allosteric modulators of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. J Med Chem. 2010;53(20):7271-9.

Heinrichs RW. The primacy of cognition in schizophrenia. Am Psychol. 2005;60(3):229-42.

[redacted]

Hughes C, Kumari V, Soni W, et al. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophr Res. 2003;59(2-3):137-46.

Javitt DC, Laruelle M. Neurochemical Theories. In: Lieberman JA, Stroup TS, Perkins DO, editors. Textbook of Schizophrenia. Washington DC: American Psychiatric Publishing; 2006. p 85-116.

Jhee S, Chappell A, Shiovitz T, et al. Multiple-dose safety and tolerability of LY450108 and LY451395 in patients with probable alzheimer's disease. Presented at the Society for Neuroscience, 2002; Washington, DC.

Jhee SS, Chappell AS, Zarotsky V, et al. Multiple-dose plasma pharmacokinetic and safety study of LY450108 and LY451395 (AMPA receptor potentiators) and their concentration in cerebrospinal fluid in healthy human subjects. J Clin Pharmacol. 2006;46(4):424-32.

Jourdi H, Yanagihara T, Martinez U, et al. Effects of positive AMPA receptor modulators on calpain-mediated spectrin degradation in cultured hippocampal slices. Neurochem Int. 2005;46(1):31-40.

Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007;64(6):633-47.

Keefe RS, Bilder RM, Harvey PD, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology. 2006;31(9):2033-46. Epub 2006/04/19.

Kiss T, Feng J, Hoffmann WE, et al. Rhythmic theta and delta activity of cortical and hippocampal neuronal networks in genetically or pharmacologically induced N-methyl-D-aspartate receptor hypofunction under urethane anesthesia. Neuroscience. 2013;237:255-67. Epub 2013/02/08.

Kremen WS, Seidman LJ, Faraone SV, et al. The paradox of normal neuropsychological function in schizophrenia. J Abnorm Psychol. 2000;109(4):743-52.

Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994;51(3):199-214.

Lynch G, Granger R, Ambros-Ingerson J, et al. Evidence that a positive modulator of AMPA-type glutamate receptors improves delayed recall in aged humans. Exp Neurol. 1997;145(1):89-92.

Lynch G, Kessler M, Rogers G, et al. Psychological effects of a drug that facilitates brain AMPA receptors. Int Clin Psychopharmacol. 1996;11(1):13-9.

Malinow R, Malenka RC. AMPA receptor trafficking and synaptic plasticity. Annu Rev Neurosci. 2002;25:103-26. Epub 2002/03/04.

Mansouri B, Henne WM, Oomman SK, et al. Involvement of calpain in AMPA-induced toxicity to rat cerebellar Purkinje neurons. Eur J Pharmacol. 2007;557(2-3):106-14. Epub 2006/11/22.

Meador-Woodruff JH, Healy DJ. Glutamate receptor expression in schizophrenic brain. Brain Res Brain Res Rev. 2000;31(2-3):288-94.

Mohn AR, Gainetdinov RR, Caron MG, et al. Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell. 1999;98(4):427-36.

Partin KM, Fleck MW, Mayer ML. AMPA receptor flip/flop mutants affecting deactivation, desensitization, and modulation by cyclothiazide, aniracetam, and thiocyanate. J Neurosci. 1996;16(21):6634-47.

Pláteník J, Kuramoto N, Yoneda Y. Molecular mechanisms associated with long-term consolidation of the NMDA signals. Life Sci. 2000;67(4):335-64.

Ranganathan M, DeMartinis N, Huguenel B, et al. Attenuation of ketamine-induced impairment in verbal learning and memory in healthy volunteers by the AMPA receptor potentiator PF-04958242. Mol Psychiatry. 2017;22(11):1633-1640. Epub 2017/02/28.

Roberts BM, Holden DE, Shaffer CL, et al. Prevention of ketamine-induced working memory impairments by AMPA potentiators in a nonhuman primate model of cognitive dysfunction. Behav Brain Res. 2010;212(1):41-8. Epub 2010/03/27.

Rosi S, Giovannini MG, Lestage PJ, et al. S 18986, a positive modulator of AMPA receptors with cognition-enhancing properties, increases ACh release in the hippocampus of young and aged rat. Neuroscience letters. 2004;361(1-3):120-3.

Rund BR, Melle I, Friis S, et al. Neurocognitive dysfunction in first-episode psychosis: correlates with symptoms, premorbid adjustment, and duration of untreated psychosis. Am J Psychiatry. 2004;161(3):466-72.

Schmitz-Hübsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology. 2006;66(11):1717-20.

Shaffer CL. Reverse and Forward Translational Neuropharmacology in Psychiatric Drug Discovery. Clin Pharmacol Ther. 2018;103(2):193-195. Epub 2017/10/27.

Shaffer CL, Hurst RS, Scialis RJ, et al. Positive allosteric modulation of AMPA receptors from efficacy to toxicity: the interspecies exposure-response continuum of the novel potentiator PF-4778574. J Pharmacol Exp Ther. 2013;347(1):212-24. Epub 2013/07/30.

Shaffer CL, Patel NC, Schwarz J, et al. The discovery and characterization of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor potentiator N-{(3S,4S)-4-[4-(5-cyano-2-thienyl)phenoxy]tetrahydrofuran-3-yl}propane-2-sulfonamide (PF-04958242). J Med Chem. 2015;58(10):4291-308. Epub 2015/05/14.

Stroup TS, Kraus JE, Marder SR. Pharmacotherapies. In: Leiberman JA, Stroup TS, O. PD, editors. Textbook of Schizophrenia. Washington DC: American Psychiatric Publishing; 2006. p 303-25.

The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

Trzepacz PT, Cummings J, Konechnik T, et al. Mibampator (LY451395) randomized clinical trial for agitation/aggression in Alzheimer's disease. Int Psychogeriatr. 2013;25(5):707-19. Epub 2012/12/21.

Ward SE, Harries M, Aldegheri L, et al. Integration of lead optimization with crystallography for a membrane-bound ion channel target: discovery of a new class of AMPA receptor positive allosteric modulators. J Med Chem. 2011;54(1):78-94. Epub 2010/12/03.

Wezenberg E, Verkes RJ, Ruigt GS, et al. Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. Neuropsychopharmacology. 2007;32(6):1272-83. Epub 2006/11/22.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 2, Randomized, Double-Blind, Multiple-Dose, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BIIB104 in Subjects With Cognitive Impairment Associated With Schizophrenia (CIAS)," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date (*DD MMM YYYY*)

_____

Investigator's Name (Print)

_____

Study Site (Print)

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 263CS201

A Phase 2, Randomized, Double-Blind, Multiple-Dose, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BIIB104 in Subjects With Cognitive Impairment Associated With Schizophrenia (CIAS)

Version 3

Date: 12 June 2019

EUDRA CT NUMBER: 2018-003825-27

IND NUMBER: 106,053

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 263CS201 is to expand the number of study sites from approximately 40 to approximately 80 and to allow the inclusion of subjects in Japan and possibly other countries.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 7, Study Design

Now reads:

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of BIIB104 in subjects with CIAS. Approximately 219 male and female subjects with stable schizophrenia from age 18 to 50 years, inclusive, will be recruited. Dosing with BIIB104 0.15 mg BID and 0.5 mg BID versus placebo will be evaluated over a treatment phase of 12 weeks. The study will be conducted at approximately ~~40~~**80** sites globally

Section 8.1, Inclusion Criteria

Now reads:

9. Must be a native ~~English~~ speaker **of the local language** and **be** able to read **at** least at a 6th grade level **(or equivalent local 11- to 12-year-old age-appropriate reading level)** as confirmed ~~by the Wide Range Assessment Test 4 – Reading (WRAT4-R) test~~ at Screening~~.~~ **by a validated reading assessment test for the local language used in the study (please refer to Study Reference Manual for appropriate local reading test).**

Rationale: These changes were made to allow additional sites from Japan and other countries to enroll subjects.

These changes also affect:

- Section 3, Sponsor Information
- Section 5, Schedules of Activities
- Section 8, Selection of Subjects
- Section 9.1.1.1, Validated Reading Test
- Section 11.4.1, Concomitant Therapy
- [redacted]
- [redacted]

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 5, Schedules of Activities, Table 3

Change: A window of up to 3 days is now allowed between completion of the Placebo Lead-In evaluation and start of dosing (Baseline/Day 1).

Now reads:

[14] The 7-day Placebo Lead-In evaluation may begin any time after eligibility has been established based on Screening assessments, provided that the Placebo Lead-In is completed no earlier than 3 days prior to the Baseline/Day 1 Visit.

Rationale: The 3-day window was added to allow flexibility in scheduling for subjects and sites and is not considered to affect the validity of the Lead-In evaluation results.

This change also affects:

- Section 7, Study Design (including Figure 1, Study 263CS201 Schematic)
- Section 9.2, Placebo Lead-In

Section 5, Schedules of Activities, Table 4 and Table 5

Change: Additional [redacted] and safety assessments were added for subjects at study sites in Japan.

Now Reads (Table 4 footnotes):

[10] For Japanese study sites only (items designated with Footnote 10 are for Japanese sites only unless otherwise specified):

- **On Day 1, in addition to baseline assessments, a [redacted] will be collected (see Table 5 for timing) and additional safety evaluations (AE recording, 12-lead ECG, brief neurological examination, and SARA) will be performed 2-hours postdose. Should any abnormal findings arise during these evaluations, an additional [redacted] will be collected. Dosing will be performed under medical supervision and observation may be extended at the Investigator's discretion prior to discharge from the site, if necessary, including an overnight stay.**
- **[redacted] and additional safety assessments 2-hours postdose (AE recording, 12-lead ECG, brief neurological exam, and SARA) will be performed.**

Now Reads ( ):

[redacted]

Rationale: As agreed with the Japanese regulatory authority, additional Japan-specific [redacted] and safety assessments were added to ensure the safety of subjects at study sites in Japan, since no Japanese subjects have previously been exposed to BIIB104 at the planned doses.

This change also affects:

- [redacted]

Section 6, Study Objectives and Endpoints

Changes: The study objectives and endpoints were changed as follows:

- [redacted]
- [redacted]
- [redacted]

Now Reads:

[redacted]

[redacted]

Rationales:

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- Section 20, References (Birchwood reference removed)

Section 7.2, Rater Qualifications

Change: The description of rater qualifications was simplified.

Now Reads:

7.2 Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Study Reference Manual. ~~The level of experience with the target population (or equivalent), and specific scale experience (or equivalent) or certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not the proposed rater can be accepted. The rater must be certified on selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted,~~

~~and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location, and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.~~It is recommended that, whenever possible, subjects and informants be interviewed and assessed throughout the study by the same rater. Reasons for changes in certified raters should be documented in the source. The Study Reference Manual provides a detailed description of specific study assessment information.

Rationale: Details that describe the process of selecting, ensuring qualifications, training, certification, recertification, and documentation of training and certification in study site records were removed from the description of rater qualifications since similar instructions are included in the Study Reference Manual.

Section 7.3, Study Stopping Rules

Change: The Diagnostic Interview for Seizure Identification form was specified as an assessment to be provided to the independent panel of neurologists in the event of suspected seizure.

Now Reads:

- All available information regarding the seizure event**, including a Diagnostic Interview for Seizure Identification form,** will be provided to an independent panel of neurologists for review and adjudication as to the diagnosis and the possible relationship to the blinded study treatment.

Rationale: This change makes explicit that the use of this form in the evaluation of possible seizures is required.

Section 8.1, Inclusion Criteria (Criterion 5)

Change: The criterion was edited to:

- make instructions for allowable antipsychotic medication dose ranges applicable to all countries and provide more detailed explanation of allowable dose ranges;
- change the allowable minor adjustments in maintenance antipsychotic therapy dose from less than 25% adjustment to less than or equal to 25% adjustment;
- change the term "psychotropic medications" to "psychiatric medications."

Now Reads:

5. Subjects must be in ongoing maintenance atypical antipsychotic therapy (except clozapine), on a stable treatment regimen for ≥~~2 months~~**8 weeks** prior to Baseline/Day 1, including concomitant ~~psychotropic treatments.~~**psychiatric medications.** Doses of

background atypical antipsychotics should be within the **recommended** dose range listed in **the** approved product labeling ~~in the US~~**of the country where the study is being conducted. Doses exceeding the recommended dose range are not permitted and doses below the recommended dose range should be discussed with the Sponsor's Medical Monitor** (see ~~the~~Section 11.4.1).

- Treatment regimen stability is defined as maintaining the same dosage of treatments except for minor adjustments (~~<~~(≤25%) to manage medication-specific tolerability issues. Recognizing that physicians outside of the study may be managing the subject's background antipsychotic and other ~~psychotropic~~**psychiatric** medications, changes in background antipsychotic and ~~psychotropic~~**psychiatric** medications should be discussed with the Sponsor's Medical Monitor.

- Stable concomitant treatment with a second atypical antipsychotic, at doses that do not exceed the **range listed in the** approved product labeling ~~in the US~~**of the country where the study is being conducted,** is permissible if used for a targeted symptom (e.g., insomnia) or an adverse effect from the primary maintenance antipsychotic treatment, but not if it is used for refractory psychotic symptoms. Treatment regimen stability as defined above applies to the second antipsychotic. Subjects should be taking no more than 2 background antipsychotics.

Rationale: The criterion was edited to accommodate the inclusion of subjects in countries outside of the United States (e.g., Japan) and to provide more specificity and greater accuracy to the language describing background antipsychotic medication and other concomitant psychiatric medication usage.

These changes also affect:

- Section 11.4.1, Concomitant Therapy

Section 8.1, Inclusion Criteria (Criterion 7)

Changes:

- The specific name of the informant interview tool for PANSS was added.

- It was specified that the in-person informant interview does not need to be conducted at the study site.

Now Reads:

7. Must have an identified informant (e.g., family member, social worker, caseworker, or nurse that spends ≥4 hours per week with the subject) who should, whenever possible, be consistent throughout the study and considered reliable by the Investigator. The

informant will provide input for completing the ~~PANSS~~**Informant Questionnaire for Positive and Negative Syndrome Scale** and SCoRS assessments. The informant needs to be able and willing to provide written informed consent and participate in at least one in-person interview (during the Screening ~~Visit~~**Period; however, the interview does not need to be conducted at the study site**) and be able to provide input in person or via the phone (for all other study visits that include ~~PANSS~~**Informant Questionnaire for Positive and Negative Syndrome Scale** and/or SCoRS assessments). Evidence of adequacy of the identified informant should be documented in source documentation. As long as both the subject visit and informant visit are within the study visit window, it is not necessary that they occur on the same day.

Rationale:

- The questionnaire name was spelled out to differentiate the Informant Questionnaire from the Structure Clinical Interview.
- The clarification on the interview timing is to allow the sites and informants greater flexibility for scheduling and conducting the informant interview.

These changes also affect:

- Section 5, Schedule of Activities (Table 3, Footnote 2; Table 4, Footnote 16)

Section 8.1, Inclusion Criteria (Criterion 12)

Change: The minimum numeric score was added for the moderate severity rating on the positive formal thought disorder item of the SCI-PANSS assessment.

Now Reads:

1. **SCI-**PANSS: No more than moderate-severe rating (score ≤5) on hallucinations, delusions, and hostility~~; PANSS~~ positive symptom items (P1, P3, P5, P6, P7), or unusual thought content (G9); and no more than a moderate severity rating **(score ≤4)** on positive formal thought disorder (P2).

Rationale: A specific score ensures that standardization of scoring occurs at all study sites.

Section 8.2, Exclusion Criteria (Criterion 3)

Change: The criterion was changed to exclude subjects who participated in any trial that used specific assessments within 6 months prior to screening.

Now Reads:

3. Participation in a ~~CIAS~~trial **that uses any component or version of MCCB or UCSD Performance-Based Skills Assessment test** within the previous 6 months.

Rationale: The change was made to narrow the scope of the exclusion to the specific tests that would affect performance in the present study.

Section 8.2, Exclusion Criteria (Criterion 5)

Change: An exclusion for subjects receiving cognitive behavioral therapy was added.

Now Reads:

5. **Participation in ongoing cognitive behavioral therapy that was initiated <8 weeks prior to Baseline/Day1.**

Rationale: Recent treatment with cognitive behavioral therapy may have an impact on efficacy response.

Section 8.2, Exclusion Criteria (Criterion 14)

Change: A numeric value for HbA1c was added to the description of exclusion for type 2 diabetes. A statement was added to clarify that type 1 diabetes is exclusionary. Some explanatory text and the reference to the study reference manual were deleted.

Now Reads:

14. Evidence or history of current clinically significant hematological, renal, endocrine (excluding adequately controlled hypothyroidism or hyperthyroidism), pulmonary (excluding chronic bronchitis, mild emphysema or chronic obstructive pulmonary disease), gastrointestinal (including conditions that can affect drug absorption, e.g., gastrectomy), oncological, dermatological, immunological disease, as determined by the Investigator in discussion with the Sponsor. Medical conditions not specifically addressed in this section may be discussed with the Sponsor's Medical Monitor to determine subject eligibility. Note that controlled type 2 diabetes ~~(as determined by current HbA1C guidelines per American Diabetes Association [ADA] criteria~~ **(HbA1c ≤7%)** will not be considered a significant medical illness and will not exclude subjects from the study; ~~see the Study Reference Manual for details of ADA criteria~~**type 1 diabetes is exclusionary.**

Rationale: This paragraph now clearly defines the definition of controlled type 2 diabetes by providing an exact numeric cutoff for HbA1c. It also highlights that type 1 diabetes is always exclusionary.

Section 8.2, Exclusion Criteria (Criterion 24)

Change: Replace "psychotropic" with "psychiatric" and provide additional detail about discontinuation of psychiatric medications prior to study entry.

Now Reads:

15. Use of prohibited treatments (see Section 11.4.1) and inability to discontinue these concomitant treatments after the Screening Visit. These treatments must be discontinued (or tapered if medically indicated) for a minimum of 5 half-lives prior to randomization at the Baseline/Day 1 Visit. Note that ~~psychotropic treatments other than~~**psychiatric medications (excluding psychiatric medications prescribed for non-psychiatric conditions and** hypnotics**)** cannot be discontinued to address this criterion due to the treatment regimen stability requirements listed in inclusion criterion 5, above.

Rationale: This change clarifies that psychiatric medications used for non-psychiatric conditions may be discontinued in order to meet study entry requirements.

Section 8.2, Exclusion Criteria (Criterion 25)

Change: An example of a type of concomitant medication that can impair cognition was added.

Now Reads:

25. Use of concomitant treatment that can impair cognition**, (e.g., centrally acting antihistamines**) as determined by the Investigator in consultation with the Sponsor.

Rationale: The example provides additional information about exclusionary concomitant medications.

Section 8.2, Exclusion Criteria (Criterion 31)

Change: Additional detail was added to the description of exclusion for hepatitis C infection.

Now Reads:

31. Current~~, acute~~ hepatitis C infection~~. Subjects with~~**(defined as** positive hepatitis C **virus [HCV]** antibody and ~~normal liver functions tests can be included~~**detectable HCV ribonucleic acid [RNA]). Subjects with positive HCV antibody and undetectable HCV RNA are eligible to participate** in the study~~(~~**(United States Centers for Disease Control and Prevention).**

Rationale: This criterion was updated for consistency with the current Biogen standard for hepatitis C exclusion.

Section 8.2, Exclusion Criteria (Criterion 37)

Change: Exclusion for previous suicide attempts was reduced from 5 years to 2 years.

Now Reads:

37. Suicide attempt within the last ~~5~~**2** years. Subjects who, in the Investigator's judgment, pose a significant suicide risk, or who have suicidal ideation associated with actual intent and a method or plan in the past 6 months (i.e., "Yes" answers on items 4 or 5 of the C-SSRS) will be excluded from the study.

Rationale: 2 years without suicide attempt is considered clinically acceptable and is consistent with other clinical studies of CIAS.

This change also affects:

- Section 14.1.4, Columbia Suicide Severity Rating Scale

Section 9.1, Screening

Change: The option for a subject's legally authorized representative to sign the informed consent was removed.

Now reads:

Subjects ~~or their legally authorized representative~~ must provide informed consent before any screening tests are performed (see Section 17.3). Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

Rationale: Only the subject may sign the informed consent.

This change also affects:

- Section 15, Safety Definitions, Recording, Reporting, and Responsibilities
- Section 17.3, Subject Information and Consent

Section 9.6, Randomization

Change: Subjects will be stratified by region.

Now reads:

Randomization will be performed using IRT. **Randomization will be stratified by region.** Subjects will be randomized in a 1:1:1 ratio to receive one of the following:

- BIIB104 0.15 mg
- BIIB104 0.5 mg
- placebo

Refer to the Study Reference Manual for additional details on randomization.

Rationale: This change will enable Biogen to investigate whether BIIB104 results in any regional differences in the primary and secondary endpoints.

This change also affects:

- Section 7, Study Design
- Section 16.1.2.1, Analysis of the Primary Endpoint
- Section 16.1.2.2, Analysis of the Secondary Endpoints

Section 14.2, Laboratory Safety Assessments

Changes:

- HbA1c will be performed only at Screening
- Testing for alcohol was added to the urine drug screen
- Editorial changes to terminology and abbreviations (no other changes in sample collection or testing)

Now reads:

The following parameters will be analyzed from ~~blood~~ samples collected from subjects at the times specified in Section 5. Samples will be analyzed using Good Laboratory Practice-validated assays.

- Complete blood count ~~(CBC)~~ including: red blood cell count, white blood cell count ~~(WBCs)~~ with differentials (neutrophils, lymphocytes, monocytes, ~~eosiniophils~~**eosinophils,** and basophils), hemoglobin, hematocrit**, platelets**, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Serum chemistry, including albumin, alkaline phosphatase, ALT, AST, BUN, **bicarbonate,** calcium, chloride, ~~carbon dioxide,~~ creatinine, creatine kinase, direct bilirubin, gamma-glutamyl transferase, glucose~~, HbA1c~~, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides, total protein, and uric acid.
- Urinalysis, including urine protein, glucose, ketones, occult blood, and ~~WBCs~~**white blood cells** by dipstick, with microscopic examination if indicated.

- **Urine drug and alcohol testing (refer to the Study Reference Manual for complete list of drugs tested)**

At Screening Visit only: testing for human immunodeficiency virus (HIV) [to be performed based upon Investigator assessment of HIV risk factors; may be omitted if not permitted by local regulations], ~~glycosylated hemoglobin, hepatitis B surface antigen, hepatitis B core antibody~~**HbA1c, HBsAg, anti-HBc,** and hepatitis C antibody; ~~alcohol/drug screen;~~and follicle-stimulating hormone (postmenopausal women only).

Rationales:

- HbA1c collection was decreased to Screening only to assess for diabetes; additional testing was considered unnecessary.
- Urine alcohol testing was added onto the urine drug screen panel to clarify and standardize the method of alcohol testing.

The addition of alcohol testing to urine drug screen affects:

- Section 5, Schedules of Activities (Table 3 and Table 4)
- Section 8.3.2, Alcohol, Caffeine, and Tobacco
- Section 14.2, Laboratory Safety Assessments

Section 17.4, Subject Data Protection

Change: A paragraph providing information about the use and disposition of audio and video recordings of clinical assessments was added to the section.

Now Reads:

Audio or video recordings may be made of some clinical assessments in order to allow for central review for standardization of test administration, where allowable by country and/or local authorities. All audio and video recordings of clinical assessments will be sent to each respective site per subject at the end of the study, kept by the vendor 1 year from last subject's last visit, then subsequently destroyed, and not sent to Biogen for archiving purposes.

Rationale: This paragraph explicitly states the use and disposition of audio and video recordings of subjects during the study.

This change also affects:

- Section 13.1, Clinical Efficacy Assessments
- Section 17.3, Subject Information and Consent

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The EUDRA CT and IND Numbers were added to the title page.
- The version number and date were updated throughout the protocol.
- The Abbreviation List was updated to reflect changes in the text of the protocol.
- Typographical errors and formatting irregularities were corrected.
- References to UPSA-B, international version, were standardized to UPSA-Bi throughout the protocol.
- Timepoints describing protocol requirements and activities, when less than 6 months, were standardized to be stated as weeks (no change in actual time, just in unit).
- In Section 5, table footnote numbering in Table 4 (Schedule of Activities – Placebo-Controlled Treatment and Safety Follow-Up) and [redacted] were adjusted to accommodate additional footnotes.
- In Section 8.2, exclusion criteria numbering was adjusted to accommodate the addition of a new criterion.
- Throughout the protocol, the assessment name of Positive and Negative Syndrome Scale (PANSS) was standardized to Structured Clinical Interview for Positive and Negative Syndrome Scale (SCI-PANSS) when administered to subjects. In one case where the PANSS is administered to the informant, it is now described as the Informant Questionnaire for PANSS.
- In Section 5, some footnotes were revised to clarify which assessments could be completed at certain times.
- The Reference List was updated to remove the citation related to the Social Functioning Scale.
- The Investigator Signature page was added at the end of the document (it was omitted from the document in Version 1 and Version 2).
- Minor clarifications of language and descriptions within the protocol, including:
  - [redacted]

- Wording was changed for minimum dosing compliance during the placebo lead-in period (no change in dosing requirement, just in how it is worded).

- In Section 11.1, the description of the total number of doses was changed from "169 doses" to "approximately 169 doses" to account for the possibility of either 1 or 2 doses on the last day of the study treatment period.

- In Section 11.4.1, to permit use of ketoconazole as a topical agent during the study.

- In Section 11.4.1, "anticonvulsants" was changed to "antiepileptics."

- [redacted]

- In Section 14.1.2, to more accurately describe the evaluations in the neurological examination.

- In Section 14.1.3, to clarify who could perform the SARA assessment.

- In Section 14.1.5, to delete erroneous text about intravenous infusion and to specify that the same arm "should be used" for blood pressure (instead of "will be used").

- In Section 14.2.2, to correct an error in the description of antipsychotic blood level collection.

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 263CS201

A Phase 2, Randomized, Double-Blind, Multiple-Dose, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BIIB104 in Subjects With Cognitive Impairment Associated With Schizophrenia (CIAS)

Version 2

Date: 10 August 2018

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 263CS201 is to decrease the duration of the study treatment period from 24 weeks to 12 weeks.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 7, Study Design

Now reads:

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of BIIB104 in subjects with CIAS. Approximately 219 male and female subjects with stable schizophrenia from age 18 to 50 years, inclusive, will be recruited. Dosing with BIIB104 0.15 mg BID and 0.5 mg BID versus placebo will be evaluated over a treatment phase of ~~up to 24~~**12** weeks. The study will be conducted at approximately 40 sites ~~in the United States~~ **globally**.

The study includes a screening phase, a placebo lead-in phase, a randomized treatment phase ~~(with 2 treatment periods)~~, and a safety follow-up (SFU) phase to begin after the last dose of study treatment. The primary analysis will be conducted after 12 weeks of placebo-controlled treatment~~(Treatment Period 1)~~. ~~Some subjects will enter the SFU phase after Treatment Period 1 and then conclude their participation in the study. It is planned that most subjects will continue placebo-controlled treatment for 12 more weeks (Treatment Period 2). Subjects who continue into Treatment Period 2 will receive an additional 12 weeks of dosing with study treatment as originally randomized (i.e., 24 weeks of continuous dosing for Treatment Periods 1 and 2 combined), with the SFU phase to occur after the last dose of study treatment.~~

~~To ensure the safety of study subjects, Treatment Period 2 of the study will not begin until 24-week data from a nonclinical toxicology study, along with any available safety data from Treatment Period 1 of the current study, have been reviewed by an Independent Data Monitoring Committee (IDMC) and it is determined that dosing up to 24 weeks has an acceptable risk-benefit profile. At the time the decision to continue with Treatment Period 2 is reached, all subjects currently in Treatment Period 1 and all subjects enrolled in the study thereafter will receive 24 weeks of continuous dosing. The 28-day follow-up phase will begin after the last dose. Note that subjects who complete the first 12 weeks of treatment (i.e., Treatment Period 1) before the determination is made by the IDMC to proceed with 24-week dosing will not participate in Treatment Period 2.~~

Screening evaluation will occur between 35 days and 8 days prior to randomization. In the 7 days prior to randomization, a placebo lead-in assessment will be conducted to evaluate the subject's ability to comply with dosing requirements. After Sponsor confirmation of eligibility and completion of baseline measurements at the Baseline/Day 1 Visit, subjects will be randomized in a 1:1:1 ratio to receive BIIB104 0.5 mg, BIIB104 0.15 mg, or placebo (planned for 73 subjects per treatment group). Subjects will be dosed at approximately 12-hour intervals for approximately 12 weeks ~~(Treatment Period 1 only) or approximately 24 weeks (Treatment~~

~~Periods 1 and 2)~~. Total duration of subject participation will be ~~up to~~ approximately ~~21~~**19** weeks ~~(Treatment Period 1 only) or approximately 33 weeks (Treatment Periods 1 and 2)~~ from screening to final follow-up visit.

See Figure 1 for a schematic presentation of the study design.

Rationale: Per regulatory agency advisement, current nonclinical data does not support the 24-week treatment period planned in Version 1 of this protocol. Therefore, the second 12 weeks of treatment (referred to as Treatment Period 2 in the original protocol) are removed from Version 2.

This change also affects:

- Section 1, Synopsis
- Section 4.4, Study Rationale
- Section 5, Schedules of Activities
- Section 6, Study Objectives and Endpoints
- Figure 1, Study 263CS201 Schematic
- Section 7.1, Study Duration for Subjects
- Section 8.3.1, Meals and Dietary
- Section 11.1, Regimen

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 7.1, Study Duration for Subjects

Change: In addition to the overall change in study treatment duration, as described in the Primary Reason for Amendment section, the duration of the safety follow-up phase was reduced from 4 weeks to 2 weeks.**Now reads:**

The maximum total duration of study participation for each subject will be ~~up to approximately 33~~ **approximately 19 weeks including a screening phase of approximately 5 weeks, a treatment phase of approximately 12 weeks, and a safety follow-up phase of approximately 2** weeks.

~~The duration of the Screening phase will be approximately 5 weeks, including a 4-week screening period and a 1-week placebo lead-in period.~~

~~The duration of Treatment Period 1 will be approximately 16 weeks including a 12-week placebo-controlled treatment phase and a 4-week SFU phase (SFU only for subjects who do not participate in Treatment Period 2). Therefore, for subjects who do not continue into Treatment Period 2, total study duration will be approximately 21 weeks.~~

~~For subjects who continue into Treatment Period 2, placebo-controlled treatment will continue for approximately 12 weeks with no pause in dosing after Treatment Period 1 (for a total of approximately 24 weeks of continuous treatment during the study). The 4-week SFU phase will begin after the last dose. Therefore, for subjects who participate in Treatment Period 2, total study duration will be approximately 33 weeks, including a 4-week screening phase, a 1-week placebo lead-in phase, a 24-week treatment phase, and a 4-week SFU phase.~~

The end of study date for a subject may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment. If the subject has ongoing AEs that are being followed, the end of study date may be the date of AE resolution.

Rationale: Based on evaluation of current clinical and nonclinical safety data, as well as the pharmacological profile of BIIB104, a 14-day safety follow-up period is considered to be an adequate post-treatment duration to assess the safety of BIIB104 following the 12-week treatment period.

This change also affects:

- Section 1, Synopsis
- Section 5, Schedules of Activities
- Section 7, Study Design
- Figure 1, Study 263CS201 Schematic
- Section 10.1, Discontinuation of Study Treatment

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting irregularities were corrected.
- In Section 7, Study Design, the location of the study was changed from "the United States" to "globally."
- A statement was added to Section 9.1.1, Screening Assessments, and Section 13.1, Clinical Efficacy Assessments, as follows: "Some ["screening" specified in 9.1.1] assessments may be recorded (see Study Reference Manual for further details)."
- In Section 8.2, exclusion criterion 22 was modified to state that marijuana use is prohibited at any time during the study.
- In Section 11.4.1, Concomitant Therapy, cognitive remediation therapy and electroconvulsive therapy were added to the list of prohibited therapies during the study (these were already listed as exclusion criteria in Section 8.2).
- In Section 14.2, Laboratory Safety Assessments, the text describing blood sample collection for the complete blood count was edited to specify white blood cell count differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).