16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

The following original protocol and protocol amendment versions were reviewed and approved by a duly constituted IRB and were implemented for this study:

Original Protocol Version 1.0, Issue Date: 21 May 2018

Protocol Version 2.0, incorporating Amendment #1, Issue Date: 02 July 2018

Protocol Version 3.0, incorporating Amendment #2, Issue Date: 28 Sep 2018

Protocol Version 4.0, incorporating Amendment #3, Issue Date: 27 Mar 2019

Protocol Version 5.0, incorporating Amendment #4, Issue Date: 24 Sep 2019

PROTOCOL

A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia

Short title: CVN058 Effect on Mismatch Negativity in Schizophrenics

Sponsor:	Cerevance Alpha (hereafter, "Cerevance") One Marina Park Drive, suite 1410 Boston, MA 02210		
Study Number:	CVN058-103		
IND Number:	121,520	**EudraCT Number:**	N/A
Compound:	CVN058		
Date:	21 MAY 2018	**Amendment Number:**	N/A

NCT Number: NCT03669250
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	[redacted]
Medical Monitor (medical advice on protocol and compound)	[redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted], MD PhD Senior Vice President Cerevance, Inc. [redacted]

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Approved by:

Signature [redacted] Date [redacted]

[redacted] MD PhD

Senior Vice President

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in the clinical trial agreement with Cerevance.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance Alpha, Inc. (hereafter referred to as "Cerevance")	**Compound:** CVN058	
Title of Protocol: A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia	**IND No.:** 121,520	**EudraCT No.:** Not Applicable
Study Number: CVN058-103	**Phase:** 1	

Study Design:

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential mismatch negativity (MMN) downstream to 5-hydroxytryptamine receptor 3 ($5\text{-}HT_3$) as a pharmacodynamic (PD) marker.

Male and female subjects with schizophrenia, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 2.a) to receive 1 of 3 dose regimens in each period: a single oral administration of CVN058 (15 mg or 150 mg) or matching placebo. The sequence will determine the order in which a subject will take each of the 3 regimens. Discontinued subjects may be replaced at the discretion of the sponsor so that approximately 20 completed subjects are available for analysis.

The study includes three 1-day treatment periods, with a minimum of 7-day washout, maximum 10 day washout (2 total washouts, after Periods 1 and 2) between periods, and a 7-10 day follow-up call post dosing of the last period. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 2.a Treatment Sequences

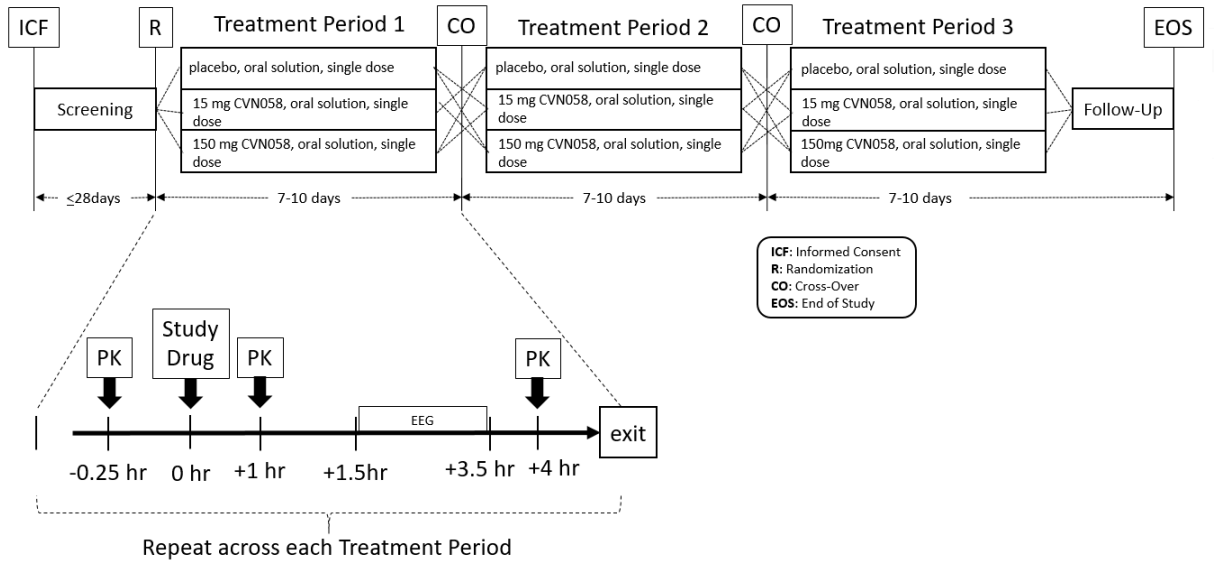
Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects undergo post dose electroencephalography (EEG) testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dosing and at various time points post dose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented below:



Primary Objective:

To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

Secondary Objective:

Assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

Exploratory Objectives:

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

Subject Population:

Subjects with stable schizophrenia on antipsychotic medication(s).

Number of Subjects:	**Number of Sites:**
Estimated total: at least 20 evaluable subjects who complete the study	Approximately 2 (United States)
Dose Level(s): Placebo: solution vehicle, oral administration CVN058: 15 mg solution, oral administration CVN058: 150 mg solution, oral administration	**Route of Administration:** Oral
Duration of Treatment: Single oral dose in each of the 3 periods.	**Period of Evaluation:** Screening Days (Part 1): Up to 28 days. 3 Treatment Periods, each <1 day duration; with a 7-10 day washout between periods Follow-up call 7-10 days following the last dose of study drug in Treatment Period 3.

	Total Duration: Up to 58 days.

Main Criteria for Inclusion:

Subjects 18 to 50 years of age, inclusive, at the time of informed consent.

The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.

Subject meets schizophrenia criteria as defined by the Diagnostic & Statistical Manual of Mental Disorders, 5th Edition (DSM–V).

Subjects are on a stable dose of antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.

Subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95.

Main Criteria for Exclusion:

Subject currently receiving treatment with any excluded medication or dietary supplement.

Subjects who have a history of gastrointestinal disease that would influence the absorption of study drug or have a history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).

Subjects having clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be not clinically significant (NCS) by the investigator at Screening

Subjects with moderate to severe substance use disorder, unstable mood or anxiety disorder.

Subject has a current diagnosis of a significant psychiatric illness other than schizophrenia per DSM-V and is in an acute phase/episode.

Subject has clinically meaningful hearing loss.

Main Criteria for Evaluation and Analyses:

Pharmacodynamics:

MMN will be measured as a PD marker for CVN058. Exploratory measurements include P50 auditory gating, gamma power, and P300, which are EEG markers commonly impaired in subjects with schizophrenia.

Pharmacokinetics:

Blood samples will be collected for the determination of plasma concentrations of CVN058, and its metabolite if appropriate, at the following time points: Pre-dose (within 15 minutes prior to dosing), and at 1 (pre-EEG) and 4 (post-EEG) hours post dose. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the curve from time 0 to the time of the last quantifiable concentration (AUC_t). Other parameters may be calculated if appropriate.

Pharmacogenomics:

Whole blood will be collected and stored for possible deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolation and analysis.

DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to variability in the PK of CVN058. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Statistical Considerations:

Observed values for the PD parameters (MMN and exploratory PD parameters) at each time point and will be summarized by treatment and compared to time matched assessments during placebo dosing using summary statistics. Comparison of post dose PD parameters to time match placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for time point, sequence,

subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the least squares mean differences between CVN058 and placebo in changes of PD parameters from time-matched period Baseline to each postdose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Plasma PK concentrations and parameters of CVN058, and its metabolite if appropriate, will be listed and summarized by treatment using descriptive statistics. Exposure-response relationships for CVN058 will be explored graphically.

Adverse events (AEs) will be presented in listings, and treatment-emergent AEs (TEAEs) will be summarized by treatment. Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Sample Size Justification:

Enrollment of 20 subjects with schizophrenia is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is expected to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HT_3	5-hydroxytryptamine (serotonin) receptor 3
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from 0 to time of last quantifiable concentration
BA	bioavailability
BMI	body mass index
CIAS	cognitive impairment associated with schizophrenia
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM -V	Diagnostic & Statistical Manual of Mental Disorders, 5th Edition – Text Revision
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalography
EMA	European Medicines Agency
ERP	evoked response potential
FDA	Food and Drug Administration
FM	Frequency-modulation
FSH	follicle-stimulating hormone
FSI	fast-spiking interneurons
F_z	frontal electrodes
F_z,C_z	frontocentral electrodes
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board

IUD	intrauterine device
K_2EDTA	potassium ethylenediamine tetraacetic acid
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMN	mismatch negativity
NCS	not clinically significant
NMDAR	N-methyl-D-aspartate receptor
NFSI	non-fasting spiking interneurons
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTE	pretreatment event
PV	parvalbumin
P_z	parietal electrodes
P50 Ratio	ratio of S2 to S1
RNA	ribonucleic acid
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SSR	steady state response
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
CVN058	also known as ENV8058 and TAK-058
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WHODRUG	World Health Organization Drug Dictionary

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a complex disorder comprising several clinical features that are highly variable among affected individuals. Probably the most well-known schizophrenia symptom domains are the so-called positive symptoms, e.g., hallucinations, delusions, disorganization of thought, bizarre behavior, and incongruity of affect. Negative symptoms include avolition (loss of motivation), blunt affect, alogia (reduced speech), and anhedonia (reduced ability to experience pleasure). Cognitive impairment associated with schizophrenia (CIAS) usually precedes psychosis and is observed in most cases involving deficits in a broad range of domains. Finally, patients with schizophrenia often experience depression and anxiety, express hostility, and become demoralized (Thaker, 2001).

Cognitive impairment is considered a core feature of schizophrenia and represents an area of significant unmet medical need. Cognitive deficits in schizophrenia include problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green, 2006). These cognitive deficits are believed to underlie much of the significant functional impairments observed in schizophrenia, such as impairment in independent living skills, social functions, vocational functioning, and self-care (Harvey, 2007). Thus, the core nature of CIAS and the associations that have been demonstrated with functional disability suggest that improving cognitive impairment may lead to improved functional outcomes (Heinrichs, 2005).

The understanding of CIAS has evolved significantly in recent years and led to new therapeutic strategies. In postmortem samples from schizophrenic patients, studies consistently reveal reduced levels of enzymes that synthesize the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the prefrontal cortex (McNally, 2013) a key center for higher cognitive function. The GABAergic neurons deficient in the cortex are termed fast-spiking interneurons (FSIs), and they express the marker parvalbumin (PV) (McNally, 2013). These PV+ FSIs are chemically coupled and release GABA in a rhythmic pattern that synchronizes the activity of local cortical pyramidal neurons (Cardin, 2009). This synchronization, which is essential for cognition, is disrupted in patients [(McNally, 2013), (Cardin, 2009)] [(Whittington, 1997), (Rotaru, 2012), (Gonzalez-Burgos, 2012)]. These and other human and animal model data implicate FSI hypofunction, and a resulting imbalance in the excitation/inhibition balance in cortical regions, in CIAS.

Based on this emerging insight into disease pathophysiology, a therapeutic that restores the normal function of the cortical pyramidal neuron/FSI microcircuit would be expected to improve cognitive function in patients with schizophrenia. One strategy for boosting the function of this circuit is to inhibit a second population of inhibitory GABAergic interneurons, known as non-fast spiking interneurons (NFSIs), which project locally onto the FSIs and the dendrites of the pyramidal neurons. These NFSIs are modulated by a wide variety of inputs, particularly excitatory glutamatergic efferents from the thalamus, and noradrenergic, cholinergic, and serotonergic efferents from subcortical regions [(Tian, 2010), (Kawaguchi, 1998), (Kawaguchi,

1997), (Lee, 2010)]. Thus, NFSIs appear to integrate state-dependent information and release GABA to regulate pyramidal neuron/FSI microcircuits.

Mismatch negativity (MMN) is an established biomarker of cortical function (Javitt, 2015). This signal is obtained as an evoked potential during an auditory oddball task, in which a subject is repeatedly exposed to auditory tones and a small proportion of those tones (the "deviant" stimuli) differ from the others (the "standard" stimuli) in their frequency or duration. Typically, the tones are presented and the evoked potentials are recorded while subjects are engaged on a different task, such as reading. Normally, the occurrence of a deviant stimulus increases the amplitude of the negative component in the evoked potential occurring at around 200 msec. MMN is the difference in amplitude between deviant and standard stimuli responses, and is considered to represent an aspect of preattentive novelty detection. MMN is consistently reduced in schizophrenia patients relative to healthy individuals, a finding extensively replicated and with a large effect size (Cohen's $d = 1$). MMN reduction in schizophrenia has been shown to reflect impaired N-methyl-D-aspartate receptor (NMDAR) function at the level of supratemporal auditory cortex, dependent on cortical interneuron modulation of pyramidal cell activity and NMDA receptor-dependent (Lee, 2017).

4.2 Non-Clinical

CVN058 (also known as ENV8058 or TAK-058) is a small molecule that potently and selectively antagonizes the 5-hydroxytryptamine (5-HT) receptor type 3 (5-HT_3). 5-HT_3 is a cys-loop family ligand-gated ion channel that allows cations to pass into the neurons when activated by serotonin, and is highly expressed in NFSIs [(Lee, 2010), (Lummis, 2012)]. The receptor is a pentamer consisting of at least two 5-HT_{3a} subunits and 3 other subunits; in the central nervous system (CNS) the receptor is almost exclusively a homomeric pentamer comprised of 5-HT_{3a} (Kawaguchi, 1997). The 5-HT_3 channel opens when serotonin molecules interact with the 2 ligand recognition sites in the extracellular side of the receptor. Influxed calcium and other positive ions depolarize the NFSIs, leading to GABA release. CVN058 is orally absorbed and readily passes the blood brain barrier, allowing it to occupy cortical 5-HT_3 receptors (50% occupancy of rat cortical 5-HT_3 receptors is achieved at plasma concentrations of approximately 5.8 ng/mL). CNS 5-HT_3 receptor occupancy is correlated with efficacy in a rat model of cognition where it reverses deficits in novel object recognition induced by subchronic phencyclidine treatment. Thus, CVN058 is a novel therapeutic candidate that may improve cognitive function by inhibiting specific subsets of cortical interneurons.

Additional information from the nonclinical studies can be found in the current Investigator's Brochure.

4.3 Clinical

Two human clinical studies of CVN058 have been completed (ENV8058_101 and TAK-058-1002).

CVN058 was well tolerated up to a dose of 150 mg administered orally as a single dose in aqueous solution (Study ENV8058_101). There were no deaths or other serious adverse events

(SAEs) reported in this study and no subject discontinued study due to a treatment-emergent adverse event (TEAE). There were no clinically significant (CS) laboratory abnormalities, electrocardiogram (ECG) changes or changes in vital signs in the completed single dose study.

The mean C_{max} and area under the plasma concentration–time curve (AUC) values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 5 to 150 mg, but mean C_{max} and AUC values increase in an approximately dose proportional manner across the 5 to 45 mg dose range. The rate of appearance of CVN058 in plasma was rapid with median time to C_{max} (t_{max}) values of 1 to 1.25 hours across the dose range of 5 to 150 mg. The mean terminal elimination half-life ($t_{1/2z}$) values of CVN058 ranged from approximately 2.8 to 10.5 hours across the cohorts; the lower doses (5 to 30 mg) had lower mean $t_{1/2z}$ values compared to the higher doses (45 to 150 mg). There were no trends with mean apparent clearance (CL/F) values of CVN058 with increasing dose from 5 to 45 mg, but faster apparent clearance was observed at the 75 and 150 mg doses, possibly due to decreased bioavailability (BA) at higher doses. The mean apparent volume of distribution (V_z/F) increased as dose increased. Excretion of unchanged CVN058 in the urine was ≤2.3% of the administered CVN058 dose over the dose range evaluated.

In the multiple-rising dose study (TAK-058-1002), CVN058 was well-tolerated at daily doses of 25, 75, and 150 mg for 7 days, and at a single 300 mg dose, in aqueous solution. There were no deaths or other SAEs reported in this study and no subject discontinued study due to a TEAE. There were no clinically significant laboratory abnormalities, ECG changes or changes in vital signs in the completed single dose study. Following single or multiple doses, the mean C_{max} and AUC values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 25 to 300 mg. No accumulation was observed following daily administration. CVN058 concentrations in cerebrospinal fluid (CSF) were assessed after daily doses of CVN058 75 mg for 5 days. The CSF concentrations averaged 17.5 ng/mL, or approximately 1% of the concentration in plasma.

4.4 Rationale for the Proposed Study

This study will explore central target engagement and proof of mechanism by measuring auditory evoked potential MMN as a pharmacodynamic (PD) marker of CNS response to the selective 5-HT_3 receptor antagonist CVN058. It has been reported that subjects with schizophrenia commonly demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50) (Javitt and Sweet, 2015). Other 5-HT_3 receptor antagonists have been reported to improve impairments in auditory evoked potentials in schizophrenic subjects. In a study with ondansetron, a 5-HT_3 receptor antagonist, using P50 auditory gating as the auditory evoked potential measure, subjects were given a single dose of ondansetron (16 mg) or placebo in a double-blind, placebo-controlled, randomized and balanced crossover design (Adler, 2005). Serial measurements of the P50 evoked potential were done at Baseline and 1, 2, and 3 hours after receipt of placebo or ondansetron. The results of the study indicated that ondansetron significantly enhanced P50 auditory gating in subjects with schizophrenia. Tropisetron, a 5-HT_3 antagonist that also has α7 nicotinic cholinergic agonist

activity, has similarly been shown to improve P50 auditory gating in subjects with schizophrenia (Koike, 2005).

While the P50 signal is likely a reflection of brainstem and thalamic network activity and is sensitive to antipsychotic treatment, MMN is thought to reflect excitation-inhibition balance in cortical circuits and is not sensitive to antipsychotic treatment (Javitt and Sweet, 2015). Therefore, to evaluate the potential for CVN058 to improve cognitive function in schizophrenics, MMN will be used as a PD marker. The study will be performed as a 3-way crossover to assess the effect on MMN of CVN058 at two dose levels relative to placebo, with each subject serving as his or her own control to reduce variability. P50 auditory gating will also be measured, as an exploratory endpoint, along with other potentially informative electrophysiological and psychometric parameters.

Medications that might inhibit or mask the effects of CVN058 will not be permitted as concomitant medications. These include serotonin reuptake inhibitors which increase synaptic serotonin levels, as well as drugs that bind to 5-HT_3 at clinically relevant concentrations or are reported to inhibit signaling through 5-HT_3 non-competitively, including some anti-psychotic drugs [(Eisensamer, 2005), (Eisensamer, 2003), (Rammes, 2004)]. Permissible anti-psychotic medications are risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

5.1.2 Secondary Objective

- To assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

5.1.3 Exploratory Objectives

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

5.2 Endpoints

5.2.1 Primary Endpoints

- Mean amplitude of duration MMN at 5 electrodes surrounding frontal (Fz) electrodes following administration of CVN058 compared to placebo.

5.2.2 Secondary Endpoint

- Percentage of subjects who experience at least 1 TEAE
- Percentage of subjects who experience at least 1 clinically significant abnormal laboratory test result

5.2.3 Exploratory Endpoints

- Mean P50 ratio (S2/S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo
- Mean P50 differences (S2-S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo.
- Pre-stimulus gamma amplitude following administration of CVN058 compared to placebo

- P300 amplitude and latency at average of 5 centroparietal electrodes around parietal electrodes (Pz) following administration of CVN058 compared to placebo
- MMN amplitude to additional deviants (frequency, intensity, location, frequency-modulation [FM]) and latency to all deviants following administration of CVN058 compared to placebo
- CVN058, its metabolite if appropriate, C_{max}, t_{max}, and area under the plasma concentration-time curve from 0 to the last quantifiable concentration (AUC_t).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential MMN downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a PD marker.

Male and female subjects with schizophrenia, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 6.a) to receive 1 of 3 dose regimens in each period; a single oral administration of CVN058 (15 mg or 150 mg), or a matching placebo. The sequence will determine the order in which a subject will receive each of the 3 regimens. Discontinued subjects may be replaced so that 20 completed subjects are available for analysis.

Each treatment period is less than 1 day in duration, with a minimum of 7-day washout, maximum 10 day washout between doses. A follow-up telephone call will occur approximately 7-10 days following the last dose received. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 6.a Treatment Sequences

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

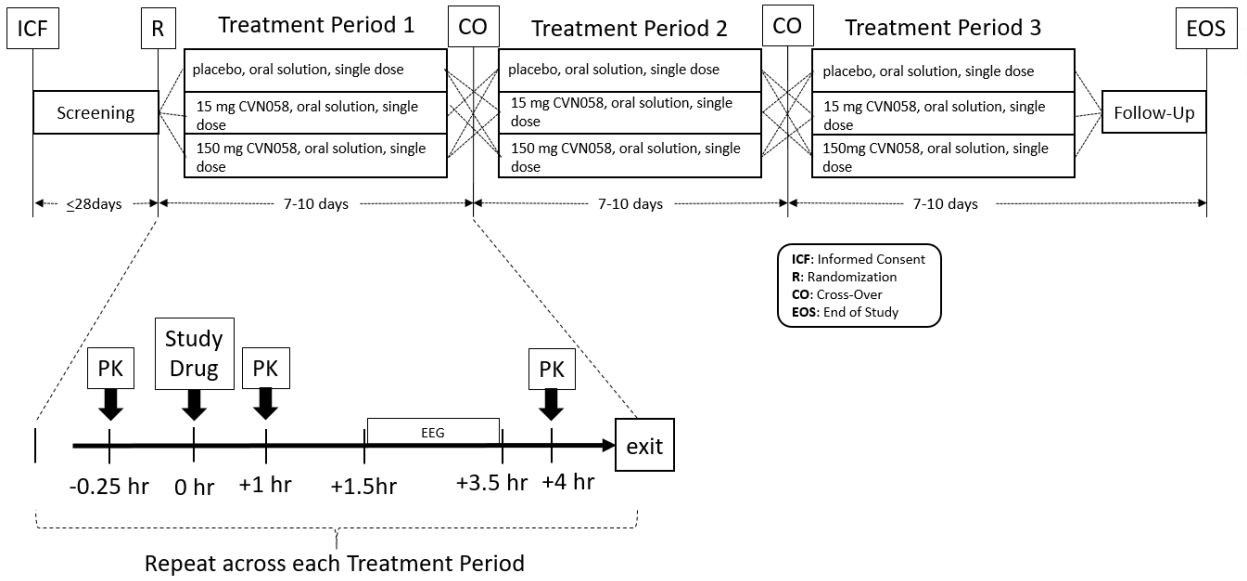
A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects will undergo post dose EEG testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water in the morning. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dose and at various time points postdose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented in Figure 6.a.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

This study will explore CNS target engagement by measuring alterations in auditory evoked potentials, similar to the demonstration of an effect on P50 auditory gating using the 5-HT_3 antagonist, ondansetron (Adler, 2005). The study design was based on that published study, adapted for CVN058 as study drug and MMN as the primary endpoint. It has been reported that most subjects with schizophrenia demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50). According to Adler et al, ondansetron improves the P50 deficit after a single dose administration (Adler, 2005).

The study will be a randomized, 3 period crossover study (CVN058 at two dose levels, and placebo) in order to evaluate the effect of CVN058 on MMN as well as on exploratory measures (i.e., P50 auditory gating, gamma power, and P300) compared to placebo. The study will be double-blind and placebo-controlled in order to avoid subjective bias in the assessment of the PD markers. In addition, conduct of study procedures for each subject will occur at approximately the same time per day across each of the Treatment Periods to avoid diurnal changes that may otherwise confound the analysis.

The 150 mg level of CVN058 is expected to saturate CNS 5-HT3 receptors throughout the EEG session, but is 50% lower than the highest dosage for which safety and tolerability has been demonstrated in previous phase 1 studies in healthy subjects, thus presumably maximizing the PD signal within the established limits of safe use. The lower dose level of 15 mg CVN058 is expected to attain a lower CNS 5-HT3 receptor occupancy, decreasing to possibly 70-80% by the end of the EEG session. The 10-fold difference in these dosages should help establish a dose-response relationship for evoked response potential (ERP) effects of CVN058. From a safety perspective, single doses ranging from 5 mg to 300 mg CVN058 have been safe and well-

tolerated. Daily doses of 25, 75, and 150 mg of CVN058 for 7 days have also been studied, and were similarly safe and well-tolerated.

The timing of dosing was selected to allow the EEG assessments to occur at the corresponding estimated t_{max} values of CVN058. The length of the washout periods is considered adequate based on the PK profile of CVN058.

In addition, based on the EEG deficits reported in subjects with schizophrenia, P50 auditory gating, gamma frequency, and P300 neurophysiological markers will be measured.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety or efficacy of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) / independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization. Subjects who do not initially meet eligibility criteria may be re-screened at investigator's discretion.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is aged 18 to 50 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.
5. The subject meets schizophrenia criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013).
6. The subject is on a stable dose of allowed antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.
7. The subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95 at Screening.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* does not agree to use adequate contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.
2. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner does not agree to use acceptable methods of contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

3. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 12 weeks after the last dose of study medication; or intending to donate ova during such time period.

4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a history of gastrointestinal disease that would influence the absorption of study drug, or history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).
6. The subject has clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be NCS by the investigator at Screening.
7. The subject has received any investigational compound within 30 days prior to signing of informed consent.
8. The subject has taken any excluded medication or dietary supplement within time frames listed in the Excluded Medications table in Section 7.3.
9. The subject does not have a stable indoor living situation (e.g., living independently, with family, or group home)
10. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
11. Subjects with moderate to severe substance use disorder according to DSM-5 criteria.
12. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use, including marijuana) at Screening.
13. The subject has a history of cancer requiring chemotherapy within the past 5 years prior to the first dose of study medication. This criterion does not include subjects successfully treated for basal cell or stage I squamous cell carcinoma of the skin.
14. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (unless having completed curative therapy), or known history of human immunodeficiency virus (HIV) antibody at Screening.
15. The subject has a QT interval with Fridericia's correction method (QTcF) >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec, confirmed by triplicate testing at 5 minute intervals, at the Screening Visit.
16. The subject has poor peripheral venous access.
17. The subject has hair or scalp condition(s) that would prevent the application of the EEG electrodes.
18. The subject has a current diagnosis of a significant psychiatric illness other than schizophrenia, per DSM-V and is in an acute phase/episode.
19. Subject has clinically meaningful hearing loss per investigator's judgment.

20. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product, within 3 months prior to Day 1.
21. The subject has an abnormal (clinically significant) Screening ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved and documented by signature of the principal investigator (PI).
22. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease, or subject with the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2x the upper limit of normal (ULN).
23. The subject has abnormal Screening vital sign values that suggest a clinically significant underlying disease.
24. The subject has a risk of suicide according to the Investigator's clinical judgment, a Screening Visit Columbia-Suicide Severity Rating Scale [C-SSRS]) score of greater than 3, or has a history of suicide attempt.

7.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a **Prohibited Medications**

28 Days Prior to Check-in	1 Days Prior to Check-in	1 Hour Prior to Each EEG Assessment
Nutraceuticals and dietary supplements (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Alcohol-containing products	Products containing nicotine, caffeine or xanthine (e.g., tea)
Antipsychotic medications, except risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega)	Sedative hypnotic medications (barbiturates and benzodiazepines)	
5-HT_3 receptor antagonists, including ondansetron (Zofran, Zuplenz), granisetron (Kytril, Sancuso, Granisol, Sustol), palonosetron (Aloxi), dolasetron (Anzemet)		
5-HT_3 allosteric modulators buproprion (Wellbutrin, Zyban) and hydroxybupropion		
Serotonin Reuptake Inhibitors (SSRI, SNRI), including sertraline (Zoloft), fluoxetine (Prozac, Sarafem), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle) , vortioxetine (Trintellix), and fluvoxamine (Luvox)		
Mirtazapine (Remeron), desipramine, imipramine, trimipramine, reboxetine		

Subjects must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting with the investigator. Subjects must be instructed to not make any changes to their concomitant medications during the course of the study without first consulting with the investigator.

During study participation, subjects will maintain usual dosing schedule of antipsychotic medication(s) and approved concomitant medications. Sedative hypnotics will not be allowed after 10 pm the night prior to testing, and until completion of testing the following day.

7.4 Diet, Fluid, Activity Control

Subjects should have their customary breakfast before each study visit. The contents of the meal should be summarized on the electronic case report form (eCRF).

During EEG and ERP assessments, subjects will remain still in a seated or partially recumbent position, according to the EEG acquisition guidelines. Subjects will refrain from strenuous exercise from 72 hours before Check-in through check-out, relative to each Treatment Period.

If subject is a smoker; they must refrain from smoking at least 1 hour prior to the EEG testing at all time points.

On each dosing day, CVN058 or placebo will be administered with approximately 240 mL of water.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 ×ULN, or
   – ALT or AST >5 ×ULN and persists for more than 2 weeks, or
   – ALT or AST >3 ×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 ×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post randomization or after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN058 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral solutions, as needed.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN058 and Matching Placebo

CVN058 drug substance is supplied as bulk powder to the clinical site to be compounded into an oral solution. A matching placebo containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor.

CVN058 oral solution will be prepared in concentrations of 10 mg/mL. The composition of the oral solutions (active and placebo) can be found in Table 8.a.

The oral solution will be labeled with the appropriate study information and caution statements.

Table 8.a Composition of CVN058 and Matching Placebo

Component	10 mg/mL solution	Placebo
CVN058 (free base)	10 g	Not Applicable
Citric Acid Monohydrate, USP	15.76 g	15.76 g
Sterile Water for Irrigation, USP	q.s. to 1,000 mL	q.s.to 1,000 mL

q.s.=quantity sufficient, USP= United States Pharmacopeia.

8.1.1.2 Sponsor-Supplied Drug

CVN058 drug substance is supplied to the clinical site by Cerevance by way of a contract manufacturing organization, Johnson-Mathey Pharma Services, Devens, MA.

8.1.1.3 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN058 powdered drug substance is stored at room temperature. CVN058 oral solution and matching placebo can be stored protected from light at 2°C-8°C (35.6°F-46.4°F) for up to 28 days. CVN058 oral solution and matching placebo are stable at room temperature for up to 24 hours.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the PI or designee, who will be blinded to the dose.

Subjects will receive CVN058 (15 mg or 150 mg) or matching placebo in each of the 3 periods.

Table 8.b describes the treatment and medication type that would be provided for each period.

Table 8.b Treatment and Medication Type

Regimen	Planned Treatment	Medication Type
A	Placebo	Placebo
B	CVN058 15 mg	CVN058
C	CVN058 150 mg	CVN058

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

The SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated, e.g., administration of supportive therapy as directed by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract and initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned a 6-digit, site specific, subject number in the sequential order in which they are randomized beginning with NNN-001, where NNN represents a site specific identifier which will be provided by the Sponsor. Replacement subjects will be assigned a new number (e.g. site number followed by subject number). The 6-digit subject number assigned will be entered in the subject's eCRF and any noted on any subject specific source record and lab sample tubes.

This 6-digit subject number will also be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.

8.3 Randomization Code Creation and Storage

The randomization schedule will be generated under the direction of Cerevance statistician or designee and a copy will be provided to the site pharmacist prior to the start of study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by contacting the dispensing pharmacist.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

No change should be made to any assessment of the subject after unblinding.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed per site's procedures.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Cerevance must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs CVN058 or placebo on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiration date and amount dispensed, including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied

drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject Screening number will be assigned to each subject at the time that the informed consent is obtained; this Screening number will be used until the subject has been randomized into the study, at which time the Subject number will be primary method of identification on study records.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

The pharmacogenomic sample collection is optional..

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, reproductive status (including last menstrual period) and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 45 days (for subjects with schizophrenia) prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the initial Screening physical examination must be assessed by the investigator as not clinically significant (NCS) or clinically significant (CS) and recorded in the source document and eCRF.

Any CS change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

The standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = weight\ (kg)/height\ (m)^2$

Note that although height is measured in centimeters, the BMI formula uses meters for height; meters can be determined by dividing centimeters by 100. Thus, for example, if height=176 cm (1.76 m) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818\ kg/m^2$.

Results for BMI will be expressed with 1 decimal place and rounding is allowed. The above value should be captured as 25.6 kg/m^2 in the database.

9.1.5 Vital Sign Procedure

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

Vital signs consisting of body temperature (oral), respiration rate, supine blood pressure and pulse will be measured in a seated resting state ($\geq$10 minutes).

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Cerevance. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or

physical examination abnormalities noted at the Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and as stipulated in the Schedule of Study Procedures (Appendix A). Abnormal Screening labs may be repeated once at the discretion of the investigator for assessment of eligibility. Subjects who still do not meet eligibility criteria may be re-screened at investigator's discretion.

Table 9.a lists the tests that will be obtained for each laboratory specimen

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets Prothrombin time /INR	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc

Diagnostic Screening:		
Serum	**Urine**	**Saliva (d)**
Serum hCG (a) At Screening Only: Hepatitis panel, including HBsAg and anti-HCV FSH (b)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c)	Alcohol cotinine

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, RBC=red blood cells, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L to obviate the need for contraception.
(c) To be performed at Screening.
(d) Alcohol and cotinine saliva samples may be collected, if needed.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

All laboratory safety data will be transferred electronically to Cerevance or designee in the format requested by Cerevance. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results into the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the PI or sub-investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, **where medications and devices containing hormones are excluded,** the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):	**Intrauterine devices (IUDs):**
Male condom PLUS spermicide.	Copper T PLUS condom or spermicide.
Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.	
Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.	

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive guidance with respect to the avoidance of pregnancy. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication. Male subjects must be advised not to donate sperm from signing of informed consent to 12 weeks after the last dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to

receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects who have only received placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded in a supine position resting for at least 10 minutes at Screening to assess eligibility. The ECGs will be recorded in triplicate at approximately 5 minute intervals. The investigator (or a qualified physician at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. A copy of the ECG trace should be kept with the subject's notes.

ECGs will be read automatically and also, the investigator or sub-investigator or a suitably qualified delegate will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal NCS, or abnormal and CS. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary.

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.12 Pharmacogenomic Sample Collection

Every subject must sign informed consent/be consented in order to participate in the study.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN058.
- Finding out more information about how CVN058 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN058.

- Identifying variations in genes related to the biological target of CVN058.

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN058 and other study medications, and for improving the efficiency, design and study methods of future research studies.

The DNA samples will be used to evaluate common variations in genes which encode drug metabolizing enzymes and transporters. This could be helpful in understanding why there are differences in CVN058 kinetics between subjects. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Whole blood will be collected and stored for possible DNA or RNA isolation and analysis.

DNA sample collection:

> One 6 mL whole blood sample will be collected before study drug dosing on Day 1 of Period 1 only from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K2EDTA) spray-coated tubes, and stored under frozen conditions.

RNA sample collection:

> Two whole blood samples (2.5 mL per sample) will be collected from each subject into a PAXgene tube on Day 1 of each period at pre dose and post EEG for RNA pharmacogenomic analysis.

If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 6-digit subject ID. Detailed instructions for the handling, shipping, and storage of pharmacogenomic samples will be provided in the lab manual.

The samples will be stored for no longer than 15 years after completion of the CVN058 study and/or until the drug development of CVN058 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Cerevance.

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) will be collected for analysis of CVN058, and its metabolite if appropriate; plasma will be collected into chilled vacutainers containing K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment will be provided in the lab manual.

Serial blood samples for determination of CVN058, and its metabolite if appropriate, in plasma will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for CVN058 Pharmacokinetic Analysis

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 15 minutes prior to dosing), 1 hour post dose (pre-EEG), and 4 hours post dose (post-EEG)

The PK samples will be collected before any other assessments are performed, if scheduled at the same time point. The actual time of sample collection will be recorded on the source document and eCRF.

Placebo samples will not be analyzed by the bioanalytical laboratory except 1 sample per subject receiving placebo around the expected time at which CVN058 C_{max} is expected to occur to ensure from a safety perspective that no subjects have inadvertently received active treatment.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of CVN058 will be measured by high-performance liquid chromatography with tandem mass spectrometry. If appropriate, plasma samples analyzed for CVN058 also may be analyzed for the CVN058 metabolite.

9.1.14 Pharmacokinetic Parameters

The PK parameters of CVN058, and its metabolite (if appropriate), will be derived using non-compartmental analysis methods. The PK parameters will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma. Other parameters may be calculated as appropriate.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
C_{max}	Maximum observed plasma concentration.
t_{max}	Time to reach C_{max}.

9.1.15 Pharmacodynamic Sample Collection

MMN will be used as a PD assessment. At each testing session, the following PD assessments will be performed during the EEG: MMN, P50, gamma power, and P300. Collection of P50 may be omitted if the essential equipment is not available. The testing session during each Treatment Period will begin approximately 1.5 hours after administration of study drug.

9.1.16 Pharmacodynamic Parameters

All EEG parameters will be obtained in accordance with the EEG acquisition guideline provided by Cerevance or their designee. It is anticipated that each EEG procedure will take approximately 3 hours to complete, including approximately 30 minutes to set up, 2 hours acquisition time, and 30 minutes to clean up.

MMN

MMN is a pre-attentive auditory component elicited by deviant stimuli in an auditory oddball task. MMN predominantly reflects activation of neuronal ensembles within primary auditory cortex, and thus indexes sensory level disturbance in schizophrenia. MMN will be obtained independently to pitch and duration deviant stimuli. MMN is maximal at frontocentral electrodes (Fz, Cz). Mean peak amplitude at 5 electrodes surrounding Fz within a predefined latency range will be the primary outcome measure.

P50

P50 auditory evoked potentials will be recorded. Participants will be seated and instructed to relax and to focus their eyes on a fixation point. Stimulus signal of 90-dB pulses of 0.1 msec in duration will be generated and recorded the event-related potential waveforms.
32 pairs of auditory clicks will be presented every 10 seconds, with a 500 msec interclick interval.

The conditioning P50 wave (S1) and test P50 wave (S2) will be identified as the power in the alpha/beta frequency bands as suggested by Smucny et al. (Smucny, 2013). The data from the vertex (Cz) and surrounding electrodes will be collected and the P50 gating ratios will be calculated as the ratio of the test P50 to the conditioning P50 power. In case the Cz gating ratio is >0.2 units above the surrounding electrodes, the value will be discarded and replaced with the value from surrounding electrodes. P50 ratio will be defined as the ratio of S2/S1 power. The S2-S1 difference score as suggested by Smucny et al. (Smucny, 2013) will be used as an exploratory outcome measure.

Quantitative Electroencephalogram, Gamma Power

Five minute eyes open/close recordings will be obtained during each recording session. Ten 1-second, artifact-free epochs will be chosen for quantitative analysis. Primary outcome measures will consist of power within delta (0.5 – 4 Hz), theta (4-7 Hz), alpha (8-13 Hz), delta (13-20 Hz), low gamma (20-40 Hz) and high gamma (40 – 60 Hz) over predesignated frontal, central, temporal and occipital sites. In addition, specific measures of 40 Hz activity will be assessed in response to repetitive 40 Hz auditory stimulation.

P300

As opposed to MMN, which are obtained under passive (i.e., no-task) conditions, auditory P300 will be obtained only when subjects must attend to and detect novel task-relevant deviant stimuli. Generators for P300 are located in distributed frontoparietal networks and so represent an index of higher order, “cognitive” processing in schizophrenia. P300 will be obtained to deviant auditory stimuli in an auditory “oddball” paradigm. P300 is maximal in amplitude at Fz and Pz

electrodes. Primary outcome measures will consist of peak amplitude within prespecified latency range at the frontal/parietal sites.

9.1.17 Positive and Negative Syndrome Scale

The PANSS was developed and standardized for typological and dimensional assessment of schizophrenic phenomena. In this study, empirically derived factors are tested excluding those items that could not be assessed during the test sessions: positive symptom factor (delusions, unusual thoughts, somatic concern, grandiosity, suspiciousness, and hallucinations), negative symptom factor (emotional withdrawal, blunted affect, poor rapport, disturbance of volition, preoccupation, and motor retardation), cognitive factor (difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgment and insight, poor attention, tension, mannerisms, and posturing), hostility (excitement, hostility, impulse control, and uncooperativeness), emotional discomfort (depression, anxiety, and guilt). PANSS will be collected at Screening, Early Termination, and at the Follow-up Visit if clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

The duration of the PANSS is approximately 30 minutes (Kay, 1990).

9.1.18 Columbia Suicide Severity Rating Scale

The determination and management of patients' suicidality risk is the Investigators' responsibility. For study purposes, suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Mundt, 2013).

The C-SSRS is a 2-page questionnaire that prospectively assesses suicidal thoughts and behavior using a structured interview for patient responses. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt).

Different versions of the scale are available. In this study, "Baseline/Screening" version will be used at Screening Visit and "Since last visit" version at all subsequent visits. "Since the last visit" should collect information from the last visit where C-SSRS was administered. If the patient's response generates a change in the findings report from negative to positive, the patient should be referred for immediate psychiatric evaluation on the same date as the site visit. Positive suicidality findings, if confirmed by the PI, is considered to be a serious event. If arising after signing informed consent but prior to administration of any study medication, it is

considered a Pretreatment Event (PTE). If arising after administration of any study medication, it is considered an SAE.

The C-SSRS will be administered by the PI or a trained designee on paper and captured in the eCRF. The same interviewer should be used throughout the study for the same subject where possible.

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail Screening should not be reused.

9.1.20 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. Randomization will take place on Day 1 of Treatment Period 1.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects with schizophrenia will be screened within 28 days prior to enrollment. All subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screen failures. Following written informed consent, Screening procedures may be conducted on different days. Assessments to be conducted during the Screening period are outlined in Appendix A.

9.3.2 Treatment Phase

The treatment will be administered over 3 Periods, separated by 7-10 days for washout. Assessments to be conducted during the screening period are outlined in Appendix A.

9.3.3 Final Visit/End of Treatment

The Final Visit additional assessments will occur prior to Discharge from the clinic at the end of Treatment Period 3, Day 1, as outlined in Appendix A.

For all subjects who received any study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The procedures outlined in Appendix A will be performed and documented.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by telephone approximately 7-10 days after receiving the last dose of study medication (Treatment Period 3) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. The genetic material will be preserved and retained by a biorepository contracted by Cerevance for up to but not longer than 15 years or as required by applicable law.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study. During the "storage" stage, the sample will be used in the analysis of the study drug and related disease states. At this stage, sample and data are linked to personal health information with code numbers. This link means that patients may be identifiable but only indirectly. The code numbers will be kept secure by the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening (x1)	Number of Samples per Period (x 3 Periods)	End of Treatment	Total Volume (mL)
Safety Laboratory Samples (a)	12.5	1	--	1	25
Hepatitis Panel	5	1	--		5
FSH (b)	3	1	--		3
PK Samples	6	--	9	--	54
DNA Sample	6	--	1 (c)	--	6
RNA Samples	5	--	6	--	30
Total Blood Sampling Volume (per Study)					123

(a) Includes Hematology, serum chemistry, and coagulation panel.

(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e. last regular menstrual cycle >2 years) and not surgically sterile.

(c) Only collected in Day 1, Period 1.

The maximum volume of blood at any single day is approximately 40 mL, and the approximate total volume of blood for the study is approximately 123 mL.

Direct venipuncture is the preferred method of blood collection. Any other method will need to be approved by the Sponsor.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if

the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.
- Suicidal Ideation and Behavior:
- A completed suicide is always a SAE based on its fatal outcome. C-SSRS score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) would likely indicate serious suicidal ideation and can be used to trigger intervention procedures to provide urgent care. Such procedures may include further evaluation and appropriate management; and/or immediate contact with (or need for a referral to) the subject's mental health practitioner; and/or possible referral to the emergency room; and/or admission to an in-subject unit. For the purpose of this protocol active suicidal ideation level 4 and 5 should be considered important medical events and reported as serious irrespective of whether the subject was hospitalized or not.
- Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or intention to act will be collected as non-serious adverse events in accordance with the standard AE reporting requirements (e.g., if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE).
- A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the eCRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as a serious adverse event.
- Acts of self-mutilation or self-injury without suicidal intention (i.e., self-imposed cigarette burns), will be collected as non-serious adverse events, unless they meet other seriousness criteria.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
   - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Medically Significant AE List (Table 10.a).

Table 10.a Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Serotonin syndrome
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.

- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE (e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE).

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication on Day 1 Period 1 of Part 2 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1 Treatment Period 1. Routine collection of AEs will continue until 21 days following last dose.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Cerevance SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).

- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Cerevance SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report, but becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products

administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Cerevance personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principle investigator must review the data change for completeness and accuracy, and must sign, and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to

enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the beginning of Part 2. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set

The Safety Set will consist of all subjects who are randomized and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration of CVN058.

Pharmacodynamic Set

The PD Set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the PK and PD endpoint analyses, but data for all subjects will be presented in the subject listings.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by sequence and overall. Summary statistics (number of subjects, mean, median, standard deviation, minimum and maximum) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, ethnicity, race, smoking status, and caffeine consumption).

13.1.3 Pharmacokinetic Analysis

The concentration of CVN058, and its metabolite if appropriate, in plasma will be summarized over each scheduled sampling interval using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

Descriptive statistics will be used to summarize the plasma PK parameters for CVN058, and its metabolite if appropriate. In addition, geometric mean and percent coefficient of variation will be computed for C_{max} and AUC_t.

A more detailed analysis will be presented in the SAP.

13.1.4 Pharmacodynamic Analysis

Observed values for the PD parameters (MMN and exploratory PD parameters) at each time point will summarized by treatment and compared to placebo using summary statistics. Comparison of post dose PD parameters from time-matched placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for time point, sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the LS mean differences between CVN058 and placebo in changes of PD parameters from time-matched period baseline to each postdose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Exposure-response relationships for CVN058 will be explored graphically.

13.1.5 Safety Analysis

The Safety Set will be used for all summaries of TEAEs, laboratory tests, and vital signs. All safety data will be summarized by treatment.

AEs will be presented in listings. TEAEs will be classified according to system organ class and preferred term and will be tabulated with a breakdown by treatment and by event severity. Similar TEAE tabulations will be performed on those events assessed by the investigator as related to study drug.

Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Physical exam findings, suicidality assessments (C-SSRS), and PANSS scores will be presented in data listings.

13.2 Determination of Sample Size

Enrollment of 20 subjects with schizophrenia is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is considered to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. PK samples collected outside of the intervals (listed in Table 14.a), ECGs, vital signs, and RNA pharmacogenomic samples collected outside of the listed intervals are minor deviations and do not require the Protocol Deviation Form to be completed but must be documented in the subject's source documents. A Protocol Deviation eCRF should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

Protocol Deviations should be captured in the site source document for PK samples collected outside of the following intervals:

Table 14.a Windows for Pharmacokinetic Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes predose	0 hour
±5	immediately postdose to ≤2 hours
±15	>2 hours

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific Screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for

purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Cerevance will, at a minimum register interventional clinical trials it sponsors on ClinicalTrials.gov or other publicly accessible websites before start of study. Cerevance contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Cerevance will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject Screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Cerevance providing this information to callers must provide Cerevance with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Cerevance may post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

		CVN058 and Placebo Treatment Periods 1, 2, and 3 (a)		End of Treatment		Follow-up
Study Day:	**Visit 1: Screening**	**Day 1 pre-dose**	**Day 1 post-dose**	**Period 3, End Day 1**	**Early Termination (c)**	**Day 7-10 After End of Treatment (b)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Medication history	X					
Physical examination	X	X		X	X	
Vital signs (d)	X	X	X		X	
Weight, height, and BMI (e)	X			X	X	
Concomitant medications (f)	X	X	X		X	X
Concurrent medical conditions (g)	X					
Clinical laboratory tests (h)	X			X	X	
Hepatitis panel	X					
Audiometric Screening (i)	X					
FSH (j)	X					
Pregnancy test (hCG), serum except as noted	X	X (urine)			X	
Urine drug and saliva alcohol screen	X					
ECG	X					
EEG battery (k)			X			
MMN (l)			X			
DNA sample collection (m)		X				
RNA sample collection (n)		X	X			
PK blood collection (o)		X	X		X	
Study drug dosing (p)			X			
PTE assessment (q)	X	X				
AE assessment (r)			X		X	X
C-SSRS (s)	X		X		X	
PANSS (t)	X		X		X	

Footnotes are on last table page.

(a) Minimum 7-day and maximum 10-day washout period is required in between Treatment Periods 1, 2 and 3.
(b) The Follow-up Visit will occur by telephone 7-10 days after End of Treatment unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Conduct procedures for subjects discontinued early per Protocol Section 7.6. The PK sample should be collected at the Early Termination Visit, if within 1 hour of a scheduled PK time point.
(d) Vital signs (oral temperature, respiration, pulse, and supine blood pressure) will be obtained at Screening, and in Periods 1, 2, and 3 (pre dose [within 30 minutes prior to dosing], and at 1 and 4 hours post dose), and at Early Termination (if applicable), and if clinically indicated according to Investigator discretion at the Follow-up visit.
(e) Height and BMI will be collected at Screening only.
(f) Record all patient medications from Screening and throughout the study.
(g) All new concurrent medical conditions arising post-oi should be recorded as PTE or AE.
(h) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening and prior to check-out at End of Treatment or Early Termination, and at the Investigator discretion if a Follow-up Visit is indicated.
(i) Audiometric Screening assessment conducted according to local practice.
(j) A FSH level will be obtained on post menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(k) For the EEG battery, testing will be done at Day 1 starting approximately 1.5 hours post dose for each period and will last approximately 2 hours. NOTE: Subjects should refrain from drinking coffee and smoking approximately 1 hour prior to the EEG assessment until discharge from clinic at the end of the afternoon.
(l) MMN will be the first EEG assessment conducted in the battery.
(m) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to study drug administration on Day 1 of Period 1 only. If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.
(n) Two 2.5 mL whole blood samples will be collected for each Period (Periods 1, 2, and 3) on Day 1 at pre-dose, and 4 hours post- dose
(o) Blood samples (6 mL) for PK analyses will be collected at pre -dose (within 15 minutes prior to dosing), and 1 and 4 hours post dose.
(p) Dosing will only occur on Day 1 of each period, and signals the start of the post-dose Day 1 visit assessments.
(q) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(r) Any adverse event with onset or exacerbation after dosing on Day 1 of Period 1 will be captured as an AE or SAE.
(s) The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered after EEG/ERP collection on each dosing day, and End of Treatment or Early Termination (if applicable).
(t) The Screening/Baseline PANSS will be collected at Screening, approximately 4 hours after each dose (post EEG) and at Early Termination (if applicable).

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form 1572) which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form 1572.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non- standard panel) Screening assessments are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CRF Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

PROTOCOL

A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia

Short title: CVN058 Effect on Mismatch Negativity in Schizophrenics

Sponsor:	Cerevance Alpha (hereafter, "Cerevance") One Marina Park Drive, suite 1410 Boston, MA 02210		
Study Number:	CVN058-103		
IND Number:	121,520	**EudraCT Number:**	N/A
Compound:	CVN058		
Date:	02 JUL 2018	**Amendment Number:**	1

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	[redacted]
Medical Monitor (medical advice on protocol and compound)	[redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted], MD PhD Senior Vice President Cerevance, Inc. [redacted]

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Approved by:

Signature [redacted] Date 02 July 2018

[redacted] MD PhD
Senior Vice President

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in the clinical trial agreement with Cerevance.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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STUDY SUMMARY

Name of Sponsor(s): Cerevance Alpha, Inc. (hereafter referred to as "Cerevance")	**Compound:** CVN058	
Title of Protocol: A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia	**IND No.:** 121,520	**EudraCT No.:** Not Applicable
Study Number: CVN058-103	**Phase:** 1	

Study Design:

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential mismatch negativity (MMN) downstream to 5-hydroxytryptamine receptor 3 ($5\text{-}HT_3$) as a pharmacodynamic (PD) marker.

Male and female subjects with schizophrenia, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 2.a) to receive 1 of 3 dose regimens in each period: a single oral administration of CVN058 (15 mg or 150 mg) or matching placebo. The sequence will determine the order in which a subject will take each of the 3 regimens. Discontinued subjects may be replaced at the discretion of the sponsor so that approximately 20 completed subjects are available for analysis.

The study includes three 1-day treatment periods, with a minimum of 7-day washout, maximum 10 day washout (2 total washouts, after Periods 1 and 2) between periods, and a 7-10 day follow-up call post dosing of the last period. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 2.a Treatment Sequences

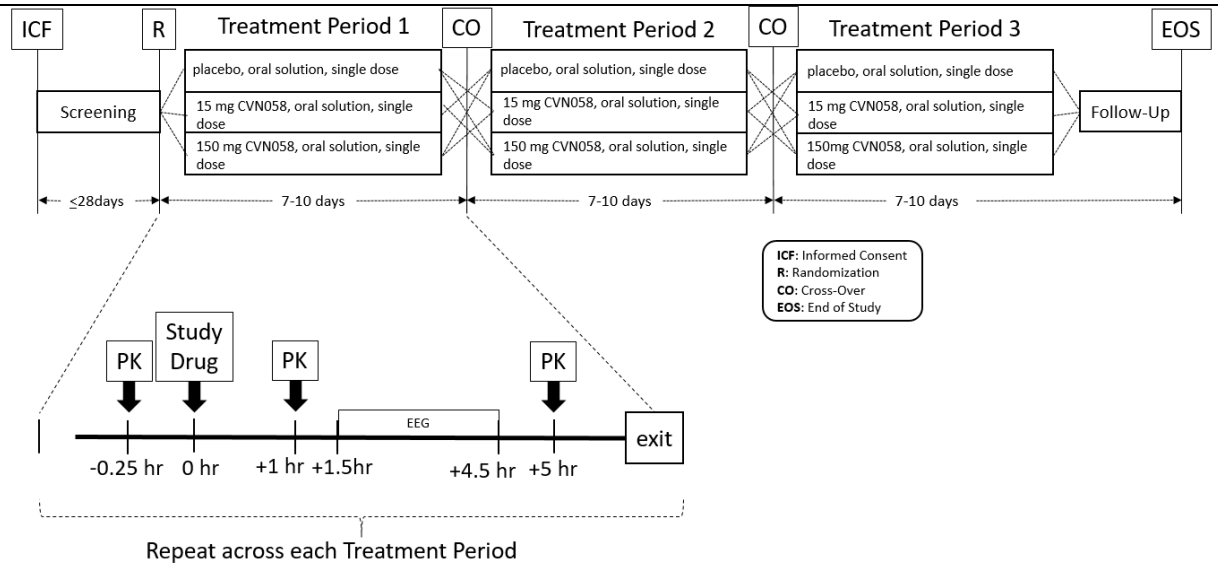
Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects undergo post dose electroencephalography (EEG) testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dosing and at various time points post dose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented below:



Primary Objective:

To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

Secondary Objective:

Assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

Exploratory Objectives:

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

Subject Population:

Subjects with stable schizophrenia on antipsychotic medication(s).

Number of Subjects:	**Number of Sites:**
Estimated total: at least 20 evaluable subjects who complete the study	Approximately 2 (United States)
Dose Level(s): Placebo: solution vehicle, oral administration CVN058: 15 mg solution, oral administration CVN058: 150 mg solution, oral administration	**Route of Administration:** Oral
Duration of Treatment: Single oral dose in each of the 3 periods.	**Period of Evaluation:** Screening Days (Part 1): Up to 28 days. 3 Treatment Periods, each <1 day duration; with a 7-10 day washout between periods Follow-up call 7-10 days following the last dose of study drug in Treatment Period 3. Total Duration: Up to 58 days.

Main Criteria for Inclusion:

Subjects 18 to 50 years of age, inclusive, at the time of informed consent.

The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.

Subject meets schizophrenia criteria as defined by the Diagnostic & Statistical Manual of Mental Disorders, 5th Edition (DSM–V).

Subjects are on a stable dose of antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.

Subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95.

Main Criteria for Exclusion:

Subject currently receiving treatment with any excluded medication or dietary supplement.

Subjects who have a history of gastrointestinal disease that would influence the absorption of study drug or have a history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).

Subjects having clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be not clinically significant (NCS) by the investigator at Screening.

Subjects with moderate to severe substance use disorder, unstable mood or anxiety disorder.

Subject has a current diagnosis of a significant psychiatric illness other than schizophrenia per DSM-V and is in an acute phase/episode.

Subject has clinically meaningful hearing loss.

Main Criteria for Evaluation and Analyses:

Pharmacodynamics:

MMN will be measured as a PD marker for CVN058. Exploratory measurements include P50 auditory gating, gamma power, and P300, which are EEG markers commonly impaired in subjects with schizophrenia.

Pharmacokinetics:

Blood samples will be collected for the determination of plasma concentrations of CVN058, and its metabolite if appropriate, at the following time points: Pre-dose (within 15 minutes prior to dosing), and at 1 (pre-EEG) and 5 (post-EEG) hours post dose. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the curve from time 0 to the time of the last quantifiable concentration (AUC_t). Other parameters may be calculated if appropriate.

Pharmacogenomics:

Whole blood will be collected and stored for possible deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolation and analysis.

DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to variability in the PK of CVN058. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Statistical Considerations:

Observed values for the PD parameters (MMN and exploratory PD parameters) at each time point and will be summarized by treatment and compared to time matched assessments during placebo dosing using summary statistics. Comparison of post dose PD parameters to time match placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for time point, sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the least squares mean differences between CVN058 and placebo in changes of PD parameters from time-matched period Baseline to each postdose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Plasma PK concentrations and parameters of CVN058, and its metabolite if appropriate, will be listed and summarized by treatment using descriptive statistics. Exposure-response relationships for CVN058 will be

explored graphically.

Adverse events (AEs) will be presented in listings, and treatment-emergent AEs (TEAEs) will be summarized by treatment. Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Sample Size Justification:

Enrollment of 20 subjects with schizophrenia is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is expected to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

2.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HT_3	5-hydroxytryptamine (serotonin) receptor 3
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from 0 to time of last quantifiable concentration
BA	bioavailability
BMI	body mass index
CIAS	cognitive impairment associated with schizophrenia
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM -V	Diagnostic & Statistical Manual of Mental Disorders, 5^{th} Edition – Text Revision
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalography
EMA	European Medicines Agency
ERP	evoked response potential
FDA	Food and Drug Administration
FM	frequency-modulation
FSH	follicle-stimulating hormone
FSI	fast-spiking interneurons
F_z	frontal electrodes
F_z,C_z	frontocentral electrodes
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	potassium ethylenediamine tetraacetic acid

LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMN	mismatch negativity
NCS	not clinically significant
NMDAR	N-methyl-D-aspartate receptor
NFSI	non-fasting spiking interneurons
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTE	pretreatment event
PV	parvalbumin
P_z	parietal electrodes
P50 Ratio	ratio of S2 to S1
RNA	ribonucleic acid
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SSR	steady state response
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
CVN058	also known as ENV8058 and TAK-058
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WHODRUG	World Health Organization Drug Dictionary

3.0 INTRODUCTION

3.1 Background

Schizophrenia is a complex disorder comprising several clinical features that are highly variable among affected individuals. Probably the most well-known schizophrenia symptom domains are the so-called positive symptoms, e.g., hallucinations, delusions, disorganization of thought, bizarre behavior, and incongruity of affect. Negative symptoms include avolition (loss of motivation), blunt affect, alogia (reduced speech), and anhedonia (reduced ability to experience pleasure). Cognitive impairment associated with schizophrenia (CIAS) usually precedes psychosis and is observed in most cases involving deficits in a broad range of domains. Finally, patients with schizophrenia often experience depression and anxiety, express hostility, and become demoralized (Thaker, 2001).

Cognitive impairment is considered a core feature of schizophrenia and represents an area of significant unmet medical need. Cognitive deficits in schizophrenia include problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green, 2006). These cognitive deficits are believed to underlie much of the significant functional impairments observed in schizophrenia, such as impairment in independent living skills, social functions, vocational functioning, and self-care (Harvey, 2007). Thus, the core nature of CIAS and the associations that have been demonstrated with functional disability suggest that improving cognitive impairment may lead to improved functional outcomes (Heinrichs, 2005).

The understanding of CIAS has evolved significantly in recent years and led to new therapeutic strategies. In postmortem samples from schizophrenic patients, studies consistently reveal reduced levels of enzymes that synthesize the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the prefrontal cortex (McNally, 2013) a key center for higher cognitive function. The GABAergic neurons deficient in the cortex are termed fast-spiking interneurons (FSIs), and they express the marker parvalbumin (PV) (McNally, 2013). These PV+ FSIs are chemically coupled and release GABA in a rhythmic pattern that synchronizes the activity of local cortical pyramidal neurons (Cardin, 2009). This synchronization, which is essential for cognition, is disrupted in patients [(McNally, 2013), (Cardin, 2009)] [(Whittington, 1997), (Rotaru, 2012), (Gonzalez-Burgos, 2012)]. These and other human and animal model data implicate FSI hypofunction, and a resulting imbalance in the excitation/inhibition balance in cortical regions, in CIAS.

Based on this emerging insight into disease pathophysiology, a therapeutic that restores the normal function of the cortical pyramidal neuron/FSI microcircuit would be expected to improve cognitive function in patients with schizophrenia. One strategy for boosting the function of this circuit is to inhibit a second population of inhibitory GABAergic interneurons, known as non-fast spiking interneurons (NFSIs), which project locally onto the FSIs and the dendrites of the pyramidal neurons. These NFSIs are modulated by a wide variety of inputs, particularly excitatory glutamatergic efferents from the thalamus, and noradrenergic, cholinergic, and serotonergic efferents from subcortical regions [(Tian, 2010), (Kawaguchi, 1998), (Kawaguchi, 1997), (Lee, 2010)]. Thus, NFSIs appear to integrate state-dependent information and release GABA to regulate pyramidal neuron/FSI microcircuits.

Mismatch negativity (MMN) is an established biomarker of cortical function (Javitt, 2015). This signal is obtained as an evoked potential during an auditory oddball task, in which a subject is

repeatedly exposed to auditory tones and a small proportion of those tones (the "deviant" stimuli) differ from the others (the "standard" stimuli) in their frequency or duration. Typically, the tones are presented and the evoked potentials are recorded while subjects are engaged on a different task, such as reading. Normally, the occurrence of a deviant stimulus increases the amplitude of the negative component in the evoked potential occurring at around 200 msec. MMN is the difference in amplitude between deviant and standard stimuli responses, and is considered to represent an aspect of preattentive novelty detection. MMN is consistently reduced in schizophrenia patients relative to healthy individuals, a finding extensively replicated and with a large effect size (Cohen's $d = 1$). MMN reduction in schizophrenia has been shown to reflect impaired N-methyl-D-aspartate receptor (NMDAR) function at the level of supratemporal auditory cortex, dependent on cortical interneuron modulation of pyramidal cell activity and NMDA receptor-dependent (Lee, 2017).

3.2 Non-Clinical

CVN058 (also known as ENV8058 or TAK-058) is a small molecule that potently and selectively antagonizes the 5-hydroxytryptamine (5-HT) receptor type 3 (5-HT_3). 5-HT_3 is a cys-loop family ligand-gated ion channel that allows cations to pass into the neurons when activated by serotonin, and is highly expressed in NFSIs [(Lee, 2010), (Lummis, 2012)]. The receptor is a pentamer consisting of at least two 5-HT_{3a} subunits and 3 other subunits; in the central nervous system (CNS) the receptor is almost exclusively a homomeric pentamer comprised of 5-HT_{3a} (Kawaguchi, 1997). The 5-HT_3 channel opens when serotonin molecules interact with the 2 ligand recognition sites in the extracellular side of the receptor. Influxed calcium and other positive ions depolarize the NFSIs, leading to GABA release. CVN058 is orally absorbed and readily passes the blood brain barrier, allowing it to occupy cortical 5-HT_3 receptors (50% occupancy of rat cortical 5-HT_3 receptors is achieved at plasma concentrations of approximately 5.8 ng/mL). CNS 5-HT_3 receptor occupancy is correlated with efficacy in a rat model of cognition where it reverses deficits in novel object recognition induced by subchronic phencyclidine treatment. Thus, CVN058 is a novel therapeutic candidate that may improve cognitive function by inhibiting specific subsets of cortical interneurons.

Additional information from the nonclinical studies can be found in the current Investigator's Brochure.

3.3 Clinical

Two human clinical studies of CVN058 have been completed (ENV8058_101 and TAK-058-1002).

CVN058 was well tolerated up to a dose of 150 mg administered orally as a single dose in aqueous solution (Study ENV8058_101). There were no deaths or other serious adverse events (SAEs) reported in this study and no subject discontinued study due to a treatment-emergent adverse event (TEAE). There were no clinically significant (CS) laboratory abnormalities, electrocardiogram (ECG) changes or changes in vital signs in the completed single dose study.

The mean C_{max} and area under the plasma concentration–time curve (AUC) values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 5 to 150 mg, but mean C_{max} and AUC values increase in an approximately dose proportional manner across the 5 to 45 mg dose range. The rate of appearance of CVN058 in plasma was rapid with

median time to C_{max} (t_{max}) values of 1 to 1.25 hours across the dose range of 5 to 150 mg. The mean terminal elimination half-life ($t_{1/2z}$) values of CVN058 ranged from approximately 2.8 to 10.5 hours across the cohorts; the lower doses (5 to 30 mg) had lower mean $t_{1/2z}$ values compared to the higher doses (45 to 150 mg). There were no trends with mean apparent clearance (CL/F) values of CVN058 with increasing dose from 5 to 45 mg, but faster apparent clearance was observed at the 75 and 150 mg doses, possibly due to decreased bioavailability (BA) at higher doses. The mean apparent volume of distribution (V_z/F) increased as dose increased. Excretion of unchanged CVN058 in the urine was ≤2.3% of the administered CVN058 dose over the dose range evaluated.

In the multiple-rising dose study (TAK-058-1002), CVN058 was well-tolerated at daily doses of 25, 75, and 150 mg for 7 days, and at a single 300 mg dose, in aqueous solution. There were no deaths or other SAEs reported in this study and no subject discontinued study due to a TEAE. There were no clinically significant laboratory abnormalities, ECG changes or changes in vital signs in the completed single dose study. Following single or multiple doses, the mean C_{max} and AUC values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 25 to 300 mg. No accumulation was observed following daily administration. CVN058 concentrations in cerebrospinal fluid (CSF) were assessed after daily doses of CVN058 75 mg for 5 days. The CSF concentrations averaged 17.5 ng/mL, or approximately 1% of the concentration in plasma.

3.4 Rationale for the Proposed Study

This study will explore central target engagement and proof of mechanism by measuring auditory evoked potential MMN as a pharmacodynamic (PD) marker of CNS response to the selective 5-HT_3 receptor antagonist CVN058. It has been reported that subjects with schizophrenia commonly demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50) (Javitt and Sweet, 2015). Other 5-HT_3 receptor antagonists have been reported to improve impairments in auditory evoked potentials in schizophrenic subjects. In a study with ondansetron, a 5-HT_3 receptor antagonist, using P50 auditory gating as the auditory evoked potential measure, subjects were given a single dose of ondansetron (16 mg) or placebo in a double-blind, placebo-controlled, randomized and balanced crossover design (Adler, 2005). Serial measurements of the P50 evoked potential were done at Baseline and 1, 2, and 3 hours after receipt of placebo or ondansetron. The results of the study indicated that ondansetron significantly enhanced P50 auditory gating in subjects with schizophrenia. Tropisetron, a 5-HT_3 antagonist that also has α7 nicotinic cholinergic agonist activity, has similarly been shown to improve P50 auditory gating in subjects with schizophrenia (Koike, 2005).

While the P50 signal is likely a reflection of brainstem and thalamic network activity and is sensitive to antipsychotic treatment, MMN is thought to reflect excitation-inhibition balance in cortical circuits and is not sensitive to antipsychotic treatment (Javitt and Sweet, 2015). Therefore, to evaluate the potential for CVN058 to improve cognitive function in schizophrenics, MMN will be used as a PD marker. The study will be performed as a 3-way crossover to assess the effect on MMN of CVN058 at two dose levels relative to placebo, with each subject serving as his or her own control to reduce variability. P50 auditory gating will also be measured, as an

exploratory endpoint, along with other potentially informative electrophysiological and psychometric parameters.

Medications that might inhibit or mask the effects of CVN058 will not be permitted as concomitant medications. These include serotonin reuptake inhibitors which increase synaptic serotonin levels, as well as drugs that bind to 5-HT_3 at clinically relevant concentrations or are reported to inhibit signaling through 5-HT_3 non-competitively, including some antipsychotic drugs [(Eisensamer, 2005), (Eisensamer, 2003), (Rammes, 2004)]. Permissible antipsychotic medications are risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega).

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

- To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

4.1.2 Secondary Objective

- To assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

4.1.3 Exploratory Objectives

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

4.2 Endpoints

4.2.1 Primary Endpoints

- Mean amplitude of duration MMN at 5 electrodes surrounding frontal (Fz) electrodes following administration of CVN058 compared to placebo.

4.2.2 Secondary Endpoint

- Percentage of subjects who experience at least 1 TEAE
- Percentage of subjects who experience at least 1 clinically significant abnormal laboratory test result

4.2.3 Exploratory Endpoints

- Mean P50 ratio (S2/S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo
- Mean P50 differences (S2-S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo.
- Pre-stimulus gamma amplitude following administration of CVN058 compared to placebo
- P300 amplitude and latency at average of 5 centroparietal electrodes around parietal electrodes (Pz) following administration of CVN058 compared to placebo

- MMN amplitude to additional deviants (frequency, intensity, location, frequency-modulation [FM]) and latency to all deviants following administration of CVN058 compared to placebo
- CVN058, its metabolite if appropriate, C_{max}, t_{max}, and area under the plasma concentration-time curve from 0 to the last quantifiable concentration (AUC_t).

5.0 STUDY DESIGN AND DESCRIPTION

5.1 Study Design

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential MMN downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a PD marker.

Male and female subjects with schizophrenia, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 6.a) to receive 1 of 3 dose regimens in each period; a single oral administration of CVN058 (15 mg or 150 mg), or a matching placebo. The sequence will determine the order in which a subject will receive each of the 3 regimens. Discontinued subjects may be replaced so that 20 completed subjects are available for analysis.

Each treatment period is less than 1 day in duration, with a minimum of 7-day washout, maximum 10 day washout between doses. A follow-up telephone call will occur approximately 7-10 days following the last dose received. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 6.a Treatment Sequences

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

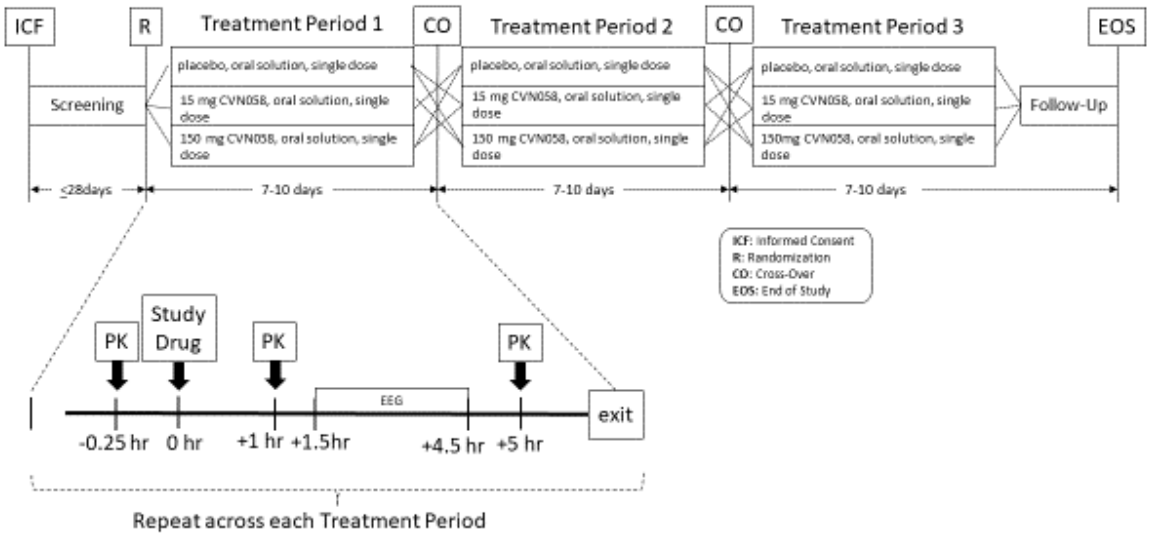
A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects will undergo post dose EEG testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water in the morning. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dose and at various time points postdose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented in Figure 6.a.

Figure 6.a Schematic of Study Design



5.2 Justification for Study Design, Dose, and Endpoints

This study will explore CNS target engagement by measuring alterations in auditory evoked potentials, similar to the demonstration of an effect on P50 auditory gating using the 5-HT_3 antagonist, ondansetron (Adler, 2005). The study design was based on that published study, adapted for CVN058 as study drug and MMN as the primary endpoint. It has been reported that most subjects with schizophrenia demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50). According to Adler et al., ondansetron improves the P50 deficit after a single dose administration (Adler, 2005).

The study will be a randomized, 3 period crossover study (CVN058 at two dose levels, and placebo) in order to evaluate the effect of CVN058 on MMN as well as on exploratory measures (i.e., P50 auditory gating, gamma power, and P300) compared to placebo. The study will be double-blind and placebo-controlled in order to avoid subjective bias in the assessment of the PD markers. In addition, conduct of study procedures for each subject will occur at approximately the same time per day across each of the Treatment Periods to avoid diurnal changes that may otherwise confound the analysis.

The 150 mg level of CVN058 is expected to saturate CNS 5-HT3 receptors throughout the EEG session, but is 50% lower than the highest dosage for which safety and tolerability has been demonstrated in previous phase 1 studies in healthy subjects, thus presumably maximizing the PD signal within the established limits of safe use. The lower dose level of 15 mg CVN058 is expected to attain a lower CNS 5-HT3 receptor occupancy, decreasing to possibly 70-80% by the end of the EEG session. The 10-fold difference in these dosages should help establish a dose-response relationship for evoked response potential (ERP) effects of CVN058. From a safety perspective, single doses ranging from 5 mg to 300 mg CVN058 have been safe and well-

tolerated. Daily doses of 25, 75, and 150 mg of CVN058 for 7 days have also been studied, and were similarly safe and well-tolerated.

The timing of dosing was selected to allow the EEG assessments to occur at the corresponding estimated t_{max} values of CVN058. The length of the washout periods is considered adequate based on the PK profile of CVN058.

In addition, based on the EEG deficits reported in subjects with schizophrenia, P50 auditory gating, gamma frequency, and P300 neurophysiological markers will be measured.

5.3 Premature Termination or Suspension of Study or Investigational Site

5.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety or efficacy of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

5.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

5.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) / independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization. Subjects who do not initially meet eligibility criteria may be re-screened at investigator's discretion.

6.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is aged 18 to 50 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.
5. The subject meets schizophrenia criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013).
6. The subject is on a stable dose of allowed antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.
7. The subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95 at Screening.

6.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* does not agree to use adequate contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.
2. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner does not agree to use acceptable methods of contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

3. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 12 weeks after the last dose of study medication; or intending to donate ova during such time period.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

5. The subject has a history of gastrointestinal disease that would influence the absorption of study drug, or history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).
6. The subject has clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be NCS by the investigator at Screening.
7. The subject has received any investigational compound within 30 days prior to signing of informed consent.
8. The subject has taken any excluded medication or dietary supplement within time frames listed in the Excluded Medications table in Section 7.3.
9. The subject does not have a stable indoor living situation (e.g., living independently, with family, or group home)
10. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
11. Subjects with moderate to severe substance use disorder according to DSM-5 criteria.
12. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use, including marijuana) at Screening.
13. The subject has a history of cancer requiring chemotherapy within the past 5 years prior to the first dose of study medication. This criterion does not include subjects successfully treated for basal cell or stage I squamous cell carcinoma of the skin.
14. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (unless having completed curative therapy), or known history of human immunodeficiency virus (HIV) antibody at Screening.
15. The subject has a QT interval with Fridericia's correction method (QTcF) >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec, confirmed by triplicate testing at 5 minute intervals, at the Screening Visit.
16. The subject has poor peripheral venous access.
17. The subject has hair or scalp condition(s) that would prevent the application of the EEG electrodes.
18. The subject has a current diagnosis of a significant psychiatric illness other than schizophrenia, per DSM-V and is in an acute phase/episode.
19. Subject has clinically meaningful hearing loss per investigator's judgment.
20. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product, within 3 months prior to Day 1.
21. The subject has an abnormal (clinically significant) Screening ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved and documented by signature of the principal investigator (PI).

22. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease, or subject with the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2x the upper limit of normal (ULN).
23. The subject has abnormal Screening vital sign values that suggest a clinically significant underlying disease.
24. The subject has a risk of suicide according to the Investigator's clinical judgment, a Screening Visit Columbia-Suicide Severity Rating Scale [C-SSRS]) score of greater than 3, or has a history of suicide attempt.

6.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a Prohibited Medications

28 Days Prior to Check-in	1 Days Prior to Check-in	1 Hour Prior to Each EEG Assessment
Nutraceuticals and dietary supplements (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Alcohol-containing products	Products containing nicotine, caffeine or xanthine (e.g., tea)
Antipsychotic medications, except risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega)	Sedative hypnotic medications (barbiturates and benzodiazepines)	
5-HT_3 receptor antagonists, including ondansetron (Zofran, Zuplenz), granisetron (Kytril, Sancuso, Granisol, Sustol), palonosetron (Aloxi), dolasetron (Anzemet)		
5-HT_3 allosteric modulators buproprion (Wellbutrin, Zyban) and hydroxybupropion		
Serotonin Reuptake Inhibitors (SSRI, SNRI), including sertraline (Zoloft), fluoxetine (Prozac, Sarafem), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle), vortioxetine (Trintellix), and fluvoxamine (Luvox)		
Mirtazapine (Remeron), desipramine, imipramine, trimipramine, reboxetine		

Subjects must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting with the investigator. Subjects must be instructed to not make any changes to their concomitant medications during the course of the study without first consulting with the investigator.

During study participation, subjects will maintain usual dosing schedule of antipsychotic medication(s) and approved concomitant medications. Sedative hypnotics will not be allowed after 10 pm the night prior to testing, and until completion of testing the following day.

6.4 Diet, Fluid, Activity Control

Subjects should have their customary breakfast before each study visit. The contents of the meal should be summarized on the electronic case report form (eCRF).

During EEG and ERP assessments, subjects will remain still in a seated or partially recumbent position, according to the EEG acquisition guidelines. Subjects will refrain from strenuous exercise from 72 hours before Check-in through check-out, relative to each Treatment Period.

If subject is a smoker; they must refrain from smoking at least 1 hour prior to the EEG testing at all time points.

On each dosing day, CVN058 or placebo will be administered with approximately 240 mL of water.

6.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 ×ULN, or
   – ALT or AST >5 ×ULN and persists for more than 2 weeks, or
   – ALT or AST >3 ×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 ×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post randomization or after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

6.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects be replaced.

7.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

7.1 Study Medication and Materials

7.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN058 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral solutions, as needed.

In this protocol, the term study medication refers to all or any of the drugs defined below.

7.1.1.1 Investigational Drug

CVN058 and Matching Placebo

CVN058 drug substance is supplied as bulk powder to the clinical site to be compounded into an oral solution. A matching placebo containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor.

CVN058 oral solution will be prepared in concentrations of 10 mg/mL. The composition of the oral solutions (active and placebo) can be found in Table 8.a.

The oral solution will be labeled with the appropriate study information and caution statements.

Table 8.a Composition of CVN058 and Matching Placebo

Component	10 mg/mL solution	Placebo
CVN058 (free base)	10 g	Not Applicable
Citric Acid Monohydrate, USP	15.76 g	15.76 g
Sterile Water for Irrigation, USP	q.s. to 1,000 mL	q.s.to 1,000 mL

q.s.=quantity sufficient, USP= United States Pharmacopeia.

7.1.1.2 Sponsor-Supplied Drug

CVN058 drug substance is supplied to the clinical site by Cerevance by way of a contract manufacturing organization, Johnson-Mathey Pharma Services, Devens, MA.

7.1.1.3 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

7.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN058 powdered drug substance is stored at room temperature. CVN058 oral solution and matching placebo can be stored protected from light at 2°C-8°C (35.6°F-46.4°F) for up to 28 days. CVN058 oral solution and matching placebo are stable at room temperature for up to 24 hours.

7.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the PI or designee, who will be blinded to the dose.

Subjects will receive CVN058 (15 mg or 150 mg) or matching placebo in each of the 3 periods.

Table 8.b describes the treatment and medication type that would be provided for each period.

Table 8.b Treatment and Medication Type

Regimen	Planned Treatment	Medication Type
A	Placebo	Placebo
B	CVN058 15 mg	CVN058
C	CVN058 150 mg	CVN058

7.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

The SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated, e.g., administration of supportive therapy as directed by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract and initiation of additional clinical monitoring.

7.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned a 7-digit subject number in the sequential order in which they are randomized beginning with a 3-digit code "NNN-" where NNN represents a site specific identifier which will be provided by the Sponsor. Replacement subjects will be assigned a new number (e.g. site number followed by subject number). The 7-digit subject number assigned will be entered in the subject's eCRF and noted on any subject specific source record and lab sample tubes.

This 7-digit subject number will also be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.

7.3 Randomization Code Creation and Storage

The randomization schedule will be generated under the direction of Cerevance statistician or designee and a copy will be provided to the site pharmacist prior to the start of study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

7.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

7.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and assignment of causality for AEs should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by contacting the dispensing pharmacist.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

No change should be made to any assessment of the subject after unblinding.

7.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed per site's procedures.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Cerevance must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs CVN058 or placebo on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiration date and amount dispensed, including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site

must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

8.0 STUDY PLAN

8.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

8.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject Screening number will be assigned to each subject at the time that the informed consent is obtained; this Screening number will be used until the subject has been randomized into the study, at which time the Subject number will be primary method of identification on study records.

8.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

The pharmacogenomic sample collection is optional.

8.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, reproductive status (including last menstrual period) and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 45 days (for subjects with schizophrenia) prior to signing of informed consent.

8.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the initial Screening physical examination must be assessed by the investigator as not clinically significant (NCS) or clinically significant (CS) and recorded in the source document and eCRF.

Any CS change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

8.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

The standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is measured in centimeters, the BMI formula uses meters for height; meters can be determined by dividing centimeters by 100. Thus, for example, if height=176 cm (1.76 m) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818\ kg/m^2$.

Results for BMI will be expressed with 1 decimal place and rounding is allowed. The above value should be captured as 25.6 kg/m^2 in the database.

8.1.5 Vital Sign Procedure

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

Vital signs consisting of body temperature (oral), respiration rate, blood pressure and pulse will be measured in a seated resting state ($\geq$10 minutes).

8.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Cerevance. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

8.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (i.e., diagnosis) should be described.

8.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and as stipulated in the Schedule of Study Procedures (Appendix A). Abnormal Screening labs may be

repeated once at the discretion of the investigator for assessment of eligibility. Subjects who still do not meet eligibility criteria may be re-screened at investigator's discretion.

Table 9.a lists the tests that will be obtained for each laboratory specimen

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets Prothrombin time /INR	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc

Diagnostic Screening:		
Serum	**Urine**	**Saliva (d)**
Serum hCG (a) At Screening Only: Hepatitis panel, including HBsAg and anti-HCV FSH (b)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c)	Alcohol cotinine

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, RBC=red blood cells, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L to obviate the need for contraception.
(c) To be performed at Screening.
(d) Alcohol and cotinine saliva samples may be collected, if needed.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

All laboratory safety data will be transferred electronically to Cerevance or designee in the format requested by Cerevance. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results into the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the PI or sub-investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

8.1.9 Contraception and Pregnancy Avoidance Procedure

During the study and for 12 weeks after last dose of study medication, nonsterilized males and female subjects of childbearing potential who are sexually active must agree to use two effective methods of contraception.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

The following are acceptable forms of contraception:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly).
- Diaphragm (plus spermicidal cream or jelly).

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.

Hormonal Contraception (stable regimen)

- Birth control pills or patch.
- Injected hormonal contraceptive (such as Depo-Provera).
- Vaginal hormonal ring (such as NuvaRing).

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive guidance with respect to the avoidance of pregnancy. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication. Male subjects must be advised not to donate sperm from signing of informed consent to 12 weeks after the last dose of study medication.

8.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects who have only received placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

8.1.11 ECG Procedure

A standard 12-lead ECG will be recorded in a supine position resting for at least 10 minutes at Screening to assess eligibility. The ECGs will be recorded in triplicate at approximately 5 minute intervals. The investigator (or a qualified physician at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. A copy of the ECG trace should be kept with the subject's notes.

ECGs will be read automatically and also, the investigator or sub-investigator or a suitably qualified delegate will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal NCS, or abnormal and CS. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary.

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

8.1.12 Pharmacogenomic Sample Collection

Every subject must sign informed consent/be consented in order to participate in the study, but consent to participate in the pharmacogenomic sample collection (genetic substudy) is optional.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN058.
- Finding out more information about how CVN058 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN058.
- Identifying variations in genes related to the biological target of CVN058.

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN058 and other study medications, and for improving the efficiency, design and study methods of future research studies.

The DNA samples will be used to evaluate common variations in genes which encode drug metabolizing enzymes and transporters. This could be helpful in understanding why there are differences in CVN058 kinetics between subjects. Also, since pharmacogenomics is an evolving

science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Whole blood will be collected and stored for possible DNA or RNA isolation and analysis.

DNA sample collection:

> One 6 mL whole blood sample will be collected before study drug dosing on Day 1 of Period 1 only from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K2EDTA) spray-coated tubes, and stored under frozen conditions.

RNA sample collection:

> Two whole blood samples (2.5 mL per sample) will be collected from each subject into a PAXgene tube on Day 1 of each period at pre dose and post EEG for RNA pharmacogenomic analysis.

If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 7-digit subject ID. Detailed instructions for the handling, shipping, and storage of pharmacogenomic samples will be provided in the lab manual.

The samples will be stored for no longer than 15 years after completion of the CVN058 study and/or until the drug development of CVN058 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Cerevance.

8.1.13 Pharmacokinetic Sample Collection

8.1.13.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) will be collected for analysis of CVN058, and its metabolite if appropriate; plasma will be collected into chilled vacutainers containing K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment will be provided in the lab manual.

Serial blood samples for determination of CVN058, and its metabolite if appropriate, in plasma will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for CVN058 Pharmacokinetic Analysis

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 15 minutes prior to dosing), 1 hour post dose (pre-EEG), and 5 hours post dose (post-EEG)

The PK samples will be collected before any other assessments are performed, if scheduled at the same time point. The actual time of sample collection will be recorded on the source document and eCRF.

Placebo samples will not be analyzed by the bioanalytical laboratory except 1 sample per subject receiving placebo around the expected time at which CVN058 C_{max} is expected to occur to ensure from a safety perspective that no subjects have inadvertently received active treatment.

8.1.13.2 Bioanalytical Methods

Plasma concentrations of CVN058 will be measured by high-performance liquid chromatography with tandem mass spectrometry. If appropriate, plasma samples analyzed for CVN058 also may be analyzed for the CVN058 metabolite.

8.1.14 Pharmacokinetic Parameters

The PK parameters of CVN058, and its metabolite (if appropriate), will be derived using non-compartmental analysis methods. The PK parameters will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma. Other parameters may be calculated as appropriate.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
C_{max}	Maximum observed plasma concentration.
t_{max}	Time to reach C_{max}.

8.1.15 Pharmacodynamic Sample Collection

MMN will be used as a PD assessment. At each testing session, the following PD assessments will be performed during the EEG: MMN, P50, gamma power, and P300. Collection of P50 may be omitted if the essential equipment is not available. The testing session during each Treatment Period will begin approximately 1.5 hours after administration of study drug.

8.1.16 Pharmacodynamic Parameters

All EEG parameters will be obtained in accordance with the EEG acquisition guideline provided by Cerevance or their designee. It is anticipated that each EEG procedure will take approximately 4 hours to complete, including approximately 30 minutes to set up, 3 hours acquisition time, and 30 minutes to clean up.

MMN

MMN is a pre-attentive auditory component elicited by deviant stimuli in an auditory oddball task. MMN predominantly reflects activation of neuronal ensembles within primary auditory cortex, and thus indexes sensory level disturbance in schizophrenia. MMN will be obtained independently to pitch and duration deviant stimuli. MMN is maximal at frontocentral electrodes (Fz, Cz). Mean peak amplitude at 5 electrodes surrounding Fz within a predefined latency range will be the primary outcome measure.

P50

P50 auditory evoked potentials will be recorded. Participants will be seated and instructed to relax and to focus their eyes on a fixation point. Stimulus signal of 90-dB pulses of 0.1 msec in duration will be generated and recorded the event-related potential waveforms.
32 pairs of auditory clicks will be presented every 10 seconds, with a 500 msec interclick interval.

The conditioning P50 wave (S1) and test P50 wave (S2) will be identified as the power in the alpha/beta frequency bands as suggested by Smucny et al. (Smucny, 2013). The data from the vertex (Cz) and surrounding electrodes will be collected and the P50 gating ratios will be calculated as the ratio of the test P50 to the conditioning P50 power. In case the Cz gating ratio is >0.2 units above the surrounding electrodes, the value will be discarded and replaced with the value from surrounding electrodes. P50 ratio will be defined as the ratio of S2/S1 power. The S2-S1 difference score as suggested by Smucny et al. (Smucny, 2013) will be used as an exploratory outcome measure.

Quantitative Electroencephalogram, Gamma Power

Five minute eyes open/close recordings will be obtained during each recording session. Ten 1-second, artifact-free epochs will be chosen for quantitative analysis. Primary outcome measures will consist of power within delta (0.5 – 4 Hz), theta (4-7 Hz), alpha (8-13 Hz), delta (13-20 Hz), low gamma (20-40 Hz) and high gamma (40 – 60 Hz) over predesignated frontal, central, temporal and occipital sites. In addition, specific measures of 40 Hz activity will be assessed in response to repetitive 40 Hz auditory stimulation.

P300

As opposed to MMN, which are obtained under passive (i.e., no-task) conditions, auditory P300 will be obtained only when subjects must attend to and detect novel task-relevant deviant stimuli. Generators for P300 are located in distributed frontoparietal networks and so represent an index of higher order, “cognitive” processing in schizophrenia. P300 will be obtained to deviant auditory stimuli in an auditory “oddball” paradigm. P300 is maximal in amplitude at Fz and Pz electrodes. Primary outcome measures will consist of peak amplitude within prespecified latency range at the frontal/parietal sites.

8.1.17 Positive and Negative Syndrome Scale

The PANSS was developed and standardized for typological and dimensional assessment of schizophrenic phenomena. In this study, empirically derived factors are tested excluding those items that could not be assessed during the test sessions: positive symptom factor (delusions, unusual thoughts, somatic concern, grandiosity, suspiciousness, and hallucinations), negative symptom factor (emotional withdrawal, blunted affect, poor rapport, disturbance of volition, preoccupation, and motor retardation), cognitive factor (difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgment and insight, poor attention, tension, mannerisms, and posturing), hostility (excitement, hostility, impulse control, and uncooperativeness), emotional discomfort (depression, anxiety, and guilt). PANSS will be collected at Screening, Early Termination, and at the Follow-up Visit if clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator’s discretion.

The duration of the PANSS is approximately 30 minutes (Kay, 1990).

8.1.18 Columbia Suicide Severity Rating Scale

The determination and management of patients' suicidality risk is the Investigators' responsibility. For study purposes, suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Mundt, 2013).

The C-SSRS is a 2-page questionnaire that prospectively assesses suicidal thoughts and behavior using a structured interview for patient responses. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt).

Different versions of the scale are available. In this study, "Baseline/Screening" version will be used at Screening Visit and "Since last visit" version at all subsequent visits. "Since the last visit" should collect information from the last visit where C-SSRS was administered. If the patient's response generates a change in the findings report from negative to positive, the patient should be referred for immediate psychiatric evaluation on the same date as the site visit. Positive suicidality findings, if confirmed by the PI, is considered to be a serious event. If arising after signing informed consent but prior to administration of any study medication, it is considered a Pretreatment Event (PTE). If arising after administration of any study medication, it is considered an SAE.

The C-SSRS will be administered by the PI or a trained designee on paper and captured in the eCRF. The same interviewer should be used throughout the study for the same subject where possible.

8.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.

- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail Screening should not be reused.

8.1.20 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. Randomization will take place on Day 1 of Treatment Period 1.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

8.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

8.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

8.3.1 Screening

Subjects with schizophrenia will be screened within 28 days prior to enrollment. All subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screen failures. Following written informed consent, Screening procedures may be conducted on different days. Assessments to be conducted during the Screening period are outlined in Appendix A.

8.3.2 Treatment Phase

The treatment will be administered over 3 Periods, separated by 7-10 days for washout. Assessments to be conducted during the screening period are outlined in Appendix A.

8.3.3 Final Visit/End of Treatment

The Final Visit additional assessments will occur prior to Discharge from the clinic at the end of Treatment Period 3, Day 1, as outlined in Appendix A.

For all subjects who received any study medication, the investigator must complete the End of Study eCRF page.

8.3.4 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The procedures outlined in Appendix A will be performed and documented.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

8.3.5 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by telephone approximately 7-10 days after receiving the last dose of study medication (Treatment Period 3) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

8.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. The genetic material will be preserved and retained by a biorepository contracted by Cerevance for up to but not longer than 15 years or as required by applicable law.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study. During the "storage" stage, the sample will be used in the analysis of the study drug and related disease states. At this stage, sample and data are linked to personal health information with code numbers. This link means that patients may be identifiable but only indirectly. The code numbers will be kept secure by the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

8.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening (x1)	Number of Samples per Period (x 3 Periods)	End of Treatment	Total Volume (mL)
Safety Laboratory Samples (a)	12.5	1	--	1	25
Hepatitis Panel	5	1	--		5
FSH (b)	3	1	--		3
PK Samples	6	--	9	--	54
DNA Sample	6	--	1 (c)	--	6
RNA Samples	5	--	6	--	30
Total Blood Sampling Volume (per Study)					123

(a) Includes Hematology, serum chemistry, and coagulation panel.

(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e. last regular menstrual cycle >2 years) and not surgically sterile.

(c) Only collected in Day 1, Period 1.

The maximum volume of blood at any single day is approximately 40 mL, and the approximate total volume of blood for the study is approximately 123 mL.

Direct venipuncture is the preferred method of blood collection. Any other method will need to be approved by the Sponsor.

9.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

9.1 Definitions

9.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.
- Suicidal Ideation and Behavior:
- A completed suicide is always a SAE based on its fatal outcome. C-SSRS score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) would likely indicate serious suicidal ideation and can be used to trigger intervention procedures to provide urgent care. Such procedures may include further evaluation and appropriate management; and/or immediate contact with (or need for a referral to) the subject's mental health practitioner; and/or possible referral to the emergency room; and/or admission to an in-subject unit. For the purpose of this protocol active suicidal ideation level 4 and 5 should be considered important medical events and reported as serious irrespective of whether the subject was hospitalized or not.
- Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or intention to act will be collected as non-serious adverse events in accordance with the standard AE reporting requirements (e.g., if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE).
- A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the eCRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as a serious adverse event.
- Acts of self-mutilation or self-injury without suicidal intention (i.e., self-imposed cigarette burns), will be collected as non-serious adverse events, unless they meet other seriousness criteria.

9.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
   - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Medically Significant AE List (Table 10.a).

Table 10.a Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Serotonin syndrome
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

9.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

9.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

9.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

9.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

9.1.10 Frequency

Episodic AEs/PTE (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

9.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE (e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE).

9.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.

- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

9.2 Procedures

9.2.1 Collection and Reporting of AEs

9.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication on Day 1 Period 1 of Part 2 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1 Treatment Period 1. Routine collection of AEs will continue until 21 days following last dose.

9.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the

eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

9.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Cerevance SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

9.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Cerevance SAE form (as per Section 10.2.2).

9.3 Follow-up of SAEs

If information is not available at the time of the first report, but becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

9.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

11.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

11.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Cerevance personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principle investigator must review the data change for completeness and accuracy, and must sign, and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore,

International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the beginning of Part 2. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

12.1.1 Analysis Sets

Safety Set

The Safety Set will consist of all subjects who are randomized and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration of CVN058.

Pharmacodynamic Set

The PD Set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the PK and PD endpoint analyses, but data for all subjects will be presented in the subject listings.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by sequence and overall. Summary statistics (number of subjects, mean, median, standard deviation, minimum and maximum) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, ethnicity, race, smoking status, and caffeine consumption).

12.1.3 Pharmacokinetic Analysis

The concentration of CVN058, and its metabolite if appropriate, in plasma will be summarized over each scheduled sampling interval using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

Descriptive statistics will be used to summarize the plasma PK parameters for CVN058, and its metabolite if appropriate. In addition, geometric mean and percent coefficient of variation will be computed for C_{max} and AUC_t.

A more detailed analysis will be presented in the SAP.

12.1.4 Pharmacodynamic Analysis

Observed values for the PD parameters (MMN and exploratory PD parameters) at each time point will summarized by treatment and compared to placebo using summary statistics. Comparison of post dose PD parameters from time-matched placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for time point, sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the LS mean differences between CVN058 and placebo in changes of PD parameters from time-matched period baseline to each postdose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Exposure-response relationships for CVN058 will be explored graphically.

12.1.5 Safety Analysis

The Safety Set will be used for all summaries of TEAEs, laboratory tests, and vital signs. All safety data will be summarized by treatment.

AEs will be presented in listings. TEAEs will be classified according to system organ class and preferred term and will be tabulated with a breakdown by treatment and by event severity. Similar TEAE tabulations will be performed on those events assessed by the investigator as related to study drug.

Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Physical exam findings, suicidality assessments (C-SSRS), and PANSS scores will be presented in data listings.

12.2 Determination of Sample Size

Enrollment of 20 subjects with schizophrenia is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is considered to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. PK samples collected outside of the intervals (listed in Table 14.a), ECGs, vital signs, and RNA pharmacogenomic samples collected outside of the listed intervals are minor deviations and do not require the Protocol Deviation Form to be completed but must be documented in the subject's source documents. A Protocol Deviation eCRF should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

Protocol Deviations should be captured in the site source document for PK samples collected outside of the following intervals:

Table 14.a Windows for Pharmacokinetic Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes predose	Pre-dose (-0.25 hour)
±5	Postdose 1 hour
±15	Postdose 5 hours

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific Screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and

benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

14.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to

the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Cerevance will, at a minimum register interventional clinical trials it sponsors on ClinicalTrials.gov or other publicly accessible websites before start of study. Cerevance contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Cerevance will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle

the trial inquiries according to their established subject Screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Cerevance providing this information to callers must provide Cerevance with a written notice requesting that their information not be listed on the registry site.

14.4.3 Clinical Trial Results Disclosure

Cerevance may post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

		CVN058 and Placebo Treatment Periods 1, 2, and 3 (a)		End of Treatment		Follow-up
Study Day:	**Visit 1: Screening**	**Day 1 pre-dose**	**Day 1 post-dose**	**Period 3, End Day 1**	**Early Termination (c)**	**Day 7-10 After End of Treatment (b)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Medication history	X					
Physical examination	X	X		X	X	
Vital signs (d)	X	X	X		X	
Weight, height, and BMI (e)	X			X	X	
Concomitant medications (f)	X	X	X		X	X
Concurrent medical conditions (g)	X					
Clinical laboratory tests (h)	X			X	X	
Hepatitis panel	X					
Audiometric Screening and Tone Matching test (i)	X					
FSH (j)	X					
Pregnancy test (hCG), serum except as noted	X	X (urine)			X	
Urine drug and saliva alcohol screen	X					
ECG	X					
EEG battery (k)			X			
MMN (l)			X			
DNA sample collection (m)		X				
RNA sample collection (n)		X	X			
PK blood collection (o)		X	X		X	
Study drug dosing (p)			X			
PTE assessment (q)	X	X				
AE assessment (r)			X		X	X
C-SSRS (s)	X		X		X	
PANSS (t)	X		X		X	

Footnotes are on last table page.

(a) Minimum 7-day and maximum 10-day washout period is required in between Treatment Periods 1, 2 and 3.
(b) The Follow-up Visit will occur by telephone 7-10 days after End of Treatment unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Conduct procedures for subjects discontinued early per Protocol Section 7.6. The PK sample should be collected at the Early Termination Visit, if within 1 hour of a scheduled PK time point.
(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, and in Periods 1, 2, and 3 (pre dose [within 30 minutes prior to dosing], and at 1 and 5 hours post dose), and at Early Termination (if applicable), and if clinically indicated according to Investigator discretion at the Follow-up visit.
(e) Height and BMI will be collected at Screening only.
(f) Record all patient medications from Screening and throughout the study.
(g) All new concurrent medical conditions arising post-oi should be recorded as PTE or AE.
(h) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening and prior to check-out at End of Treatment or Early Termination, and at the Investigator discretion if a Follow-up Visit is indicated.
(i) Audiometric Screening assessment conducted according to local practice.
(j) A FSH level will be obtained on post menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(k) For the EEG battery, testing will be done at Day 1 starting approximately 1.5 hours post dose for each period and will last approximately 3 hours. NOTE: Subjects should refrain from drinking coffee and smoking approximately 1 hour prior to the EEG assessment until discharge from clinic at the end of the afternoon.
(l) MMN will be the first EEG assessment conducted in the battery.
(m) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to study drug administration on Day 1 of Period 1 only. If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.
(n) Two 2.5 mL whole blood samples will be collected for each Period (Periods 1, 2, and 3) on Day 1 at pre-dose, and 5 hours post-dose.
(o) Blood samples (6 mL) for PK analyses will be collected at pre -dose (within 15 minutes prior to dosing), and 1 and 5 hours post dose.
(p) Dosing will only occur on Day 1 of each period, and signals the start of the post-dose Day 1 visit assessments.
(q) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(r) Any adverse event with onset or exacerbation after dosing on Day 1 of Period 1 will be captured as an AE or SAE.
(s) The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered after EEG/ERP collection on each dosing day, and End of Treatment or Early Termination (if applicable).
(t) The Screening/Baseline PANSS will be collected at Screening, approximately 5 hours after each dose (post EEG) and at Early Termination (if applicable).

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form 1572) which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form 1572.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non- standard panel) Screening assessments are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CRF Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

PROTOCOL

A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia

Short title: CVN058 Effect on Mismatch Negativity in Schizophrenics

Sponsor:	Cerevance Alpha (hereafter, "Cerevance") One Marina Park Drive, suite 1410 Boston, MA 02210		
Study Number:	CVN058-103		
IND Number:	121,520	**EudraCT Number:**	N/A
Compound:	CVN058		
Date:	28 Sep 2018	**Amendment Number:**	2
Previous Versions:			
	02 Jul 2018	**Amendment Number:**	1
	21 May 2018	**Original**	

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	[redacted]
Medical Monitor (carries overall responsibility for the conduct of the study)	[redacted], MD, CPI Director of Medical Affairs, CliniLabs [redacted]
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD PhD Senior Vice President Cerevance, Inc. [redacted]

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Approved by:

Signatur[redacted] Date [redacted]

[redacted] MD PhD[redacted]
Senior Vice President

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in the clinical trial agreement with Cerevance.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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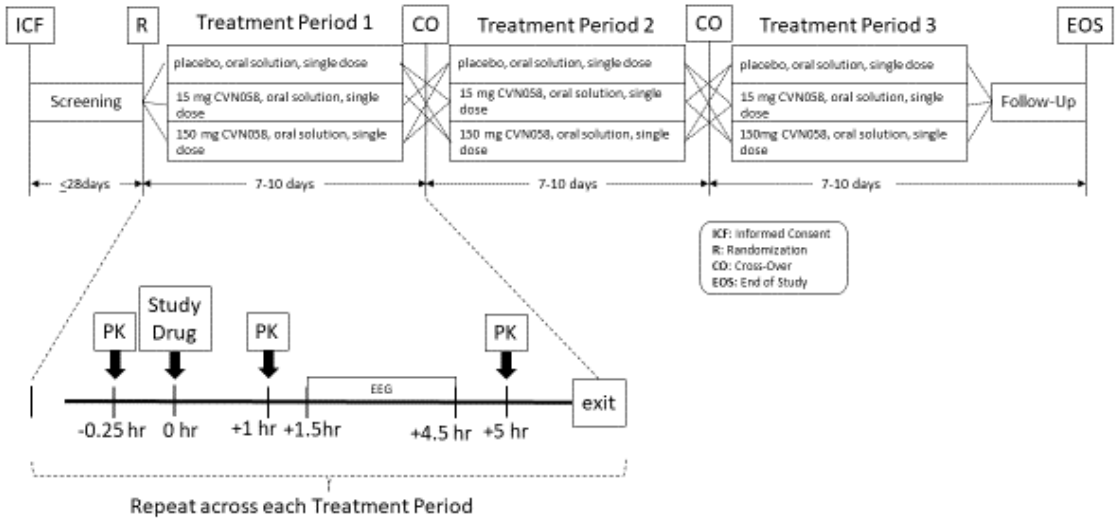
2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Cerevance Alpha, Inc.
(hereafter referred to as “Cerevance”)</td><td colspan="2">Compound:
CVN058</td></tr>
<tr><td>Title of Protocol: A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia</td><td>IND No.: 121,520</td><td colspan="2">EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Number: CVN058-103</td><td colspan="3">Phase: 1</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential mismatch negativity (MMN) downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a pharmacodynamic (PD) marker.</td></tr>
<tr><td colspan="4">Male and female subjects with schizophrenia, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 2.a) to receive 1 of 3 dose regimens in each period: a single oral administration of CVN058 (15 mg or 150 mg) or matching placebo. The sequence will determine the order in which a subject will take each of the 3 regimens. Discontinued subjects may be replaced at the discretion of the sponsor so that approximately 20 completed subjects are available for analysis.
The study includes three 1-day treatment periods, with a minimum of 7-day washout, maximum 10 day washout (2 total washouts, after Periods 1 and 2) between periods, and a 7-10 day follow-up call post dosing of the last period. Subjects may be inpatients or outpatients at the discretion of the Investigator.
Table 2.a Treatment Sequences
<table>
<tr><th>Sequence</th><th>Period 1</th><th>Period 2</th><th>Period 3</th></tr>
<tr><td>1</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>2</td><td>B</td><td>A</td><td>C</td></tr>
<tr><td>3</td><td>C</td><td>A</td><td>B</td></tr>
<tr><td>4</td><td>A</td><td>C</td><td>B</td></tr>
<tr><td>5</td><td>B</td><td>C</td><td>A</td></tr>
<tr><td>6</td><td>C</td><td>B</td><td>A</td></tr>
</table>
A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg
At each testing session, subjects undergo post dose electroencephalography (EEG) testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dosing and at various time points post dose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.
Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented below:</td></tr>
</table>



Primary Objective:

To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

Secondary Objective:

Assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

Exploratory Objectives:

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

Subject Population:

Subjects with stable schizophrenia on antipsychotic medication(s).

Number of Subjects:	**Number of Sites:**
Estimated total: at least 20 evaluable subjects who complete the study	Approximately 2 (United States)
Dose Level(s): Placebo: solution vehicle, oral administration CVN058: 15 mg solution, oral administration CVN058: 150 mg solution, oral administration	**Route of Administration:** Oral
Duration of Treatment: Single oral dose in each of the 3 periods.	**Period of Evaluation:** Screening Days (Part 1): Up to 28 days. 3 Treatment Periods, each <1 day duration; with a 7-10 day washout between periods Follow-up call 7-10 days following the last dose of

	study drug in Treatment Period 3. Total Duration: Up to 58 days.

Main Criteria for Inclusion:

Subjects 18 to 50 years of age, inclusive, at the time of informed consent.

The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.

Subject meets schizophrenia criteria as defined by the Diagnostic & Statistical Manual of Mental Disorders, 5th Edition (DSM–V).

Subjects are on a stable dose of antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.

Subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95.

Main Criteria for Exclusion:

Subject currently receiving treatment with any excluded medication or dietary supplement.

Subjects who have a history of gastrointestinal disease that would influence the absorption of study drug or have a history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).

Subjects having clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be not clinically significant (NCS) by the investigator at Screening.

Subjects with moderate to severe substance use disorder, unstable mood or anxiety disorder.

Subject has a current diagnosis of a significant psychiatric illness other than schizophrenia per DSM-V and is in an acute phase/episode.

Subject has clinically meaningful hearing loss.

Main Criteria for Evaluation and Analyses:

Pharmacodynamics:

MMN will be measured as a PD marker for CVN058. Exploratory measurements include P50 auditory gating, gamma power, and P300, which are EEG markers commonly impaired in subjects with schizophrenia.

Pharmacokinetics:

Blood samples will be collected for the determination of plasma concentrations of CVN058, and its metabolite if appropriate, at the following time points: Pre-dose (within 15 minutes prior to dosing), and at 1 (pre-EEG) and 5 (post-EEG) hours post dose. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the curve from time 0 to the time of the last quantifiable concentration (AUC_t). Other parameters may be calculated if appropriate.

Pharmacogenomics:

Whole blood will be collected and stored for possible deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolation and analysis.

DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to variability in the PK of CVN058. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Statistical Considerations:

Observed values for the PD parameters (MMN and exploratory PD parameters) at each time point and will be summarized by treatment and compared to time matched assessments during placebo dosing using summary statistics. Comparison of post dose PD parameters to time match placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for time point, sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed

for the least squares mean differences between CVN058 and placebo in changes of PD parameters from time-matched period Baseline to each postdose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Plasma PK concentrations and parameters of CVN058, and its metabolite if appropriate, will be listed and summarized by treatment using descriptive statistics. Exposure-response relationships for CVN058 will be explored graphically.

Adverse events (AEs) will be presented in listings, and treatment-emergent AEs (TEAEs) will be summarized by treatment. Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Sample Size Justification:

Enrollment of 20 subjects with schizophrenia is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is expected to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HT_3	5-hydroxytryptamine (serotonin) receptor 3
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from 0 to time of last quantifiable concentration
BA	bioavailability
BMI	body mass index
CIAS	cognitive impairment associated with schizophrenia
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM -V	Diagnostic & Statistical Manual of Mental Disorders, 5^{th} Edition – Text Revision
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalography
EMA	European Medicines Agency
ERP	evoked response potential
FDA	Food and Drug Administration
FM	frequency-modulation
FSH	follicle-stimulating hormone
FSI	fast-spiking interneurons
F_z	frontal electrodes
F_z,C_z	frontocentral electrodes
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device

K_2EDTA	potassium ethylenediamine tetraacetic acid
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMN	mismatch negativity
NCS	not clinically significant
NMDAR	N-methyl-D-aspartate receptor
NFSI	non-fasting spiking interneurons
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
PTE	pretreatment event
PV	parvalbumin
P_z	parietal electrodes
P50 Ratio	ratio of S2 to S1
RNA	ribonucleic acid
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SSR	steady state response
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
CVN058	also known as ENV8058 and TAK-058
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WHODRUG	World Health Organization Drug Dictionary

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a complex disorder comprising several clinical features that are highly variable among affected individuals. Probably the most well-known schizophrenia symptom domains are the so-called positive symptoms, e.g., hallucinations, delusions, disorganization of thought, bizarre behavior, and incongruity of affect. Negative symptoms include avolition (loss of motivation), blunt affect, alogia (reduced speech), and anhedonia (reduced ability to experience pleasure). Cognitive impairment associated with schizophrenia (CIAS) usually precedes psychosis and is observed in most cases involving deficits in a broad range of domains. Finally, patients with schizophrenia often experience depression and anxiety, express hostility, and become demoralized (Thaker, 2001).

Cognitive impairment is considered a core feature of schizophrenia and represents an area of significant unmet medical need. Cognitive deficits in schizophrenia include problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green, 2006). These cognitive deficits are believed to underlie much of the significant functional impairments observed in schizophrenia, such as impairment in independent living skills, social functions, vocational functioning, and self-care (Harvey, 2007). Thus, the core nature of CIAS and the associations that have been demonstrated with functional disability suggest that improving cognitive impairment may lead to improved functional outcomes (Heinrichs, 2005).

The understanding of CIAS has evolved significantly in recent years and led to new therapeutic strategies. In postmortem samples from schizophrenic patients, studies consistently reveal reduced levels of enzymes that synthesize the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the prefrontal cortex (McNally, 2013) a key center for higher cognitive function. The GABAergic neurons deficient in the cortex are termed fast-spiking interneurons (FSIs), and they express the marker parvalbumin (PV) (McNally, 2013). These PV+ FSIs are chemically coupled and release GABA in a rhythmic pattern that synchronizes the activity of local cortical pyramidal neurons (Cardin, 2009). This synchronization, which is essential for cognition, is disrupted in patients [(McNally, 2013), (Cardin, 2009)] [(Whittington, 1997), (Rotaru, 2012), (Gonzalez-Burgos, 2012)]. These and other human and animal model data implicate FSI hypofunction, and a resulting imbalance in the excitation/inhibition balance in cortical regions, in CIAS.

Based on this emerging insight into disease pathophysiology, a therapeutic that restores the normal function of the cortical pyramidal neuron/FSI microcircuit would be expected to improve cognitive function in patients with schizophrenia. One strategy for boosting the function of this circuit is to inhibit a second population of inhibitory GABAergic interneurons, known as non-fast spiking interneurons (NFSIs), which project locally onto the FSIs and the dendrites of the pyramidal neurons. These NFSIs are modulated by a wide variety of inputs, particularly excitatory glutamatergic efferents from the thalamus, and noradrenergic, cholinergic, and serotonergic efferents from subcortical regions [(Tian, 2010), (Kawaguchi, 1998), (Kawaguchi, 1997), (Lee, 2010)]. Thus, NFSIs appear to integrate state-dependent information and release GABA to regulate pyramidal neuron/FSI microcircuits.

Mismatch negativity (MMN) is an established biomarker of cortical function (Javitt, 2015). This signal is obtained as an evoked potential during an auditory oddball task, in which a subject is repeatedly exposed to auditory tones and a small proportion of those tones (the "deviant" stimuli) differ from the others (the "standard" stimuli) in their frequency or duration. Typically, the tones are presented and the evoked potentials are recorded while subjects are engaged on a different task, such as reading. Normally, the occurrence of a deviant stimulus increases the amplitude of the negative component in the evoked potential occurring at around 200 msec. MMN is the difference in amplitude between deviant and standard stimuli responses, and is considered to represent an aspect of preattentive novelty detection. MMN is consistently reduced in schizophrenia patients relative to healthy individuals, a finding extensively replicated and with a large effect size (Cohen's $d = 1$). MMN reduction in schizophrenia has been shown to reflect impaired N-methyl-D-aspartate receptor (NMDAR) function at the level of supratemporal auditory cortex, dependent on cortical interneuron modulation of pyramidal cell activity and NMDA receptor-dependent (Lee, 2017).

4.2 Non-Clinical

CVN058 (also known as ENV8058 or TAK-058) is a small molecule that potently and selectively antagonizes the 5-hydroxytryptamine (5-HT) receptor type 3 (5-HT_3). 5-HT_3 is a cys-loop family ligand-gated ion channel that allows cations to pass into the neurons when activated by serotonin, and is highly expressed in NFSIs [(Lee, 2010), (Lummis, 2012)]. The receptor is a pentamer consisting of at least two 5-HT_{3a} subunits and 3 other subunits; in the central nervous system (CNS) the receptor is almost exclusively a homomeric pentamer comprised of 5-HT_{3a} (Kawaguchi, 1997). The 5-HT_3 channel opens when serotonin molecules interact with the 2 ligand recognition sites in the extracellular side of the receptor. Influxed calcium and other positive ions depolarize the NFSIs, leading to GABA release. CVN058 is orally absorbed and readily passes the blood brain barrier, allowing it to occupy cortical 5-HT_3 receptors (50% occupancy of rat cortical 5-HT_3 receptors is achieved at plasma concentrations of approximately 5.8 ng/mL). CNS 5-HT_3 receptor occupancy is correlated with efficacy in a rat model of cognition where it reverses deficits in novel object recognition induced by subchronic phencyclidine treatment. Thus, CVN058 is a novel therapeutic candidate that may improve cognitive function by inhibiting specific subsets of cortical interneurons.

Additional information from the nonclinical studies can be found in the current Investigator's Brochure.

4.3 Clinical

Two human clinical studies of CVN058 have been completed (ENV8058_101 and TAK-058-1002).

CVN058 was well tolerated up to a dose of 150 mg administered orally as a single dose in aqueous solution (Study ENV8058_101). There were no deaths or other serious adverse events (SAEs) reported in this study and no subject discontinued study due to a treatment-emergent adverse event (TEAE). There were no clinically significant (CS) laboratory abnormalities, electrocardiogram (ECG) changes or changes in vital signs in the completed single dose study.

The mean C_{max} and area under the plasma concentration–time curve (AUC) values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 5 to 150 mg, but mean C_{max} and AUC values increase in an approximately dose proportional manner across the 5 to 45 mg dose range. The rate of appearance of CVN058 in plasma was rapid with median time to C_{max} (t_{max}) values of 1 to 1.25 hours across the dose range of 5 to 150 mg. The mean terminal elimination half-life ($t_{1/2z}$) values of CVN058 ranged from approximately 2.8 to 10.5 hours across the cohorts; the lower doses (5 to 30 mg) had lower mean $t_{1/2z}$ values compared to the higher doses (45 to 150 mg). There were no trends with mean apparent clearance (CL/F) values of CVN058 with increasing dose from 5 to 45 mg, but faster apparent clearance was observed at the 75 and 150 mg doses, possibly due to decreased bioavailability (BA) at higher doses. The mean apparent volume of distribution (V_z/F) increased as dose increased. Excretion of unchanged CVN058 in the urine was ≤2.3% of the administered CVN058 dose over the dose range evaluated.

In the multiple-rising dose study (TAK-058-1002), CVN058 was well-tolerated at daily doses of 25, 75, and 150 mg for 7 days, and at a single 300 mg dose, in aqueous solution. There were no deaths or other SAEs reported in this study and no subject discontinued study due to a TEAE. There were no clinically significant laboratory abnormalities, ECG changes or changes in vital signs in the completed single dose study. Following single or multiple doses, the mean C_{max} and AUC values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 25 to 300 mg. No accumulation was observed following daily administration. CVN058 concentrations in cerebrospinal fluid (CSF) were assessed after daily doses of CVN058 75 mg for 5 days. The CSF concentrations averaged 17.5 ng/mL, or approximately 1% of the concentration in plasma.

4.4 Rationale for the Proposed Study

This study will explore central target engagement and proof of mechanism by measuring auditory evoked potential MMN as a pharmacodynamic (PD) marker of CNS response to the selective 5-HT_3 receptor antagonist CVN058. It has been reported that subjects with schizophrenia commonly demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50) (Javitt and Sweet, 2015). Other 5-HT_3 receptor antagonists have been reported to improve impairments in auditory evoked potentials in schizophrenic subjects. In a study with ondansetron, a 5-HT_3 receptor antagonist, using P50 auditory gating as the auditory evoked potential measure, subjects were given a single dose of ondansetron (16 mg) or placebo in a double-blind, placebo-controlled, randomized and balanced crossover design (Adler, 2005). Serial measurements of the P50 evoked potential were done at Baseline and 1, 2, and 3 hours after receipt of placebo or ondansetron. The results of the study indicated that ondansetron significantly enhanced P50 auditory gating in subjects with schizophrenia. Tropisetron, a 5-HT_3 antagonist that also has α7 nicotinic cholinergic agonist activity, has similarly been shown to improve P50 auditory gating in subjects with schizophrenia (Koike, 2005).

While the P50 signal is likely a reflection of brainstem and thalamic network activity and is sensitive to antipsychotic treatment, MMN is thought to reflect excitation-inhibition balance in cortical circuits and is not sensitive to antipsychotic treatment (Javitt and Sweet, 2015). Therefore, to evaluate the potential for CVN058 to improve cognitive function in schizophrenics,

MMN will be used as a PD marker. The study will be performed as a 3-way crossover to assess the effect on MMN of CVN058 at two dose levels relative to placebo, with each subject serving as his or her own control to reduce variability. P50 auditory gating will also be measured, as an exploratory endpoint, along with other potentially informative electrophysiological and psychometric parameters.

Medications that might inhibit or mask the effects of CVN058 will not be permitted as concomitant medications. These include serotonin reuptake inhibitors which increase synaptic serotonin levels, as well as drugs that bind to 5-HT_3 at clinically relevant concentrations or are reported to inhibit signaling through 5-HT_3 non-competitively, including some antipsychotic drugs [(Eisensamer, 2005), (Eisensamer, 2003), (Rammes, 2004)]. Permissible antipsychotic medications are risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

5.1.2 Secondary Objective

- To assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

5.1.3 Exploratory Objectives

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

5.2 Endpoints

5.2.1 Primary Endpoints

- Mean amplitude of duration MMN at 5 electrodes surrounding frontal (Fz) electrodes following administration of CVN058 compared to placebo.

5.2.2 Secondary Endpoint

- Percentage of subjects who experience at least 1 TEAE
- Percentage of subjects who experience at least 1 clinically significant abnormal laboratory test result

5.2.3 Exploratory Endpoints

- Mean P50 ratio (S2/S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo
- Mean P50 differences (S2-S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo.
- Pre-stimulus gamma amplitude following administration of CVN058 compared to placebo
- P300 amplitude and latency at average of 5 centroparietal electrodes around parietal electrodes (Pz) following administration of CVN058 compared to placebo

- MMN amplitude to additional deviants (frequency, intensity, location, frequency-modulation [FM]) and latency to all deviants following administration of CVN058 compared to placebo
- CVN058, its metabolite if appropriate, C_{max}, t_{max}, and area under the plasma concentration-time curve from 0 to the last quantifiable concentration (AUC_t).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential MMN downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a PD marker.

Male and female subjects with schizophrenia, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 6.a) to receive 1 of 3 dose regimens in each period; a single oral administration of CVN058 (15 mg or 150 mg), or a matching placebo. The sequence will determine the order in which a subject will receive each of the 3 regimens. Discontinued subjects may be replaced so that 20 completed subjects are available for analysis.

Each treatment period is less than 1 day in duration, with a minimum of 7-day washout, maximum 10 day washout between doses. A follow-up telephone call will occur approximately 7-10 days following the last dose received. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 6.a Treatment Sequences

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

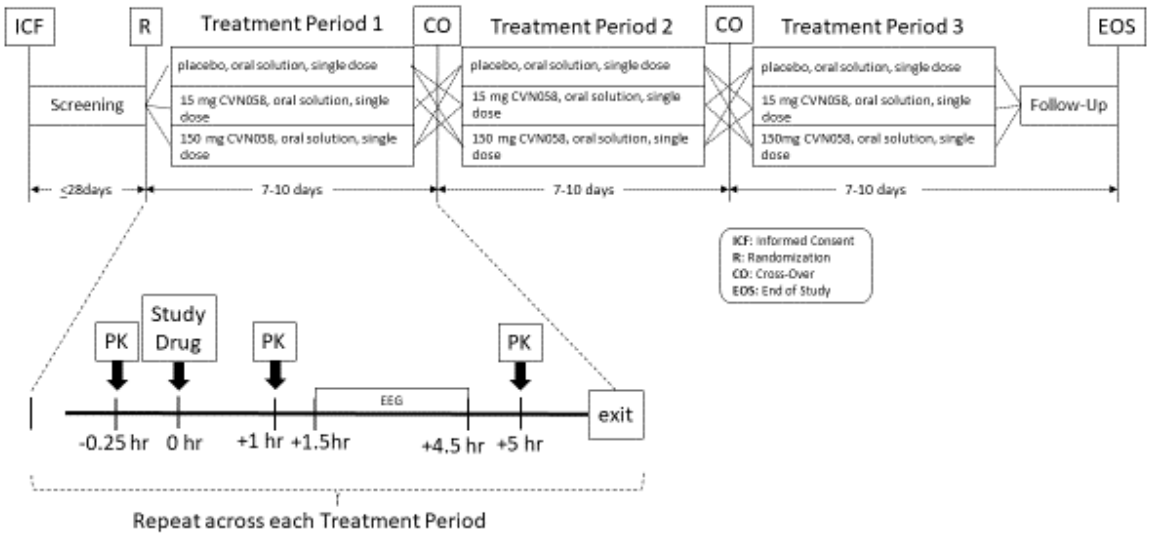
A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects will undergo post dose EEG testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water in the morning. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dose and at various time points postdose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented in Figure 6.a.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

This study will explore CNS target engagement by measuring alterations in auditory evoked potentials, similar to the demonstration of an effect on P50 auditory gating using the 5-HT_3 antagonist, ondansetron (Adler, 2005). The study design was based on that published study, adapted for CVN058 as study drug and MMN as the primary endpoint. It has been reported that most subjects with schizophrenia demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50). According to Adler et al., ondansetron improves the P50 deficit after a single dose administration (Adler, 2005).

The study will be a randomized, 3 period crossover study (CVN058 at two dose levels, and placebo) in order to evaluate the effect of CVN058 on MMN as well as on exploratory measures (i.e., P50 auditory gating, gamma power, and P300) compared to placebo. The study will be double-blind and placebo-controlled in order to avoid subjective bias in the assessment of the PD markers. In addition, conduct of study procedures for each subject will occur at approximately the same time per day across each of the Treatment Periods to avoid diurnal changes that may otherwise confound the analysis.

The 150 mg level of CVN058 is expected to saturate CNS 5-HT3 receptors throughout the EEG session, but is 50% lower than the highest dosage for which safety and tolerability has been demonstrated in previous phase 1 studies in healthy subjects, thus presumably maximizing the PD signal within the established limits of safe use. The lower dose level of 15 mg CVN058 is expected to attain a lower CNS 5-HT3 receptor occupancy, decreasing to possibly 70-80% by the end of the EEG session. The 10-fold difference in these dosages should help establish a dose-response relationship for evoked response potential (ERP) effects of CVN058. From a safety

perspective, single doses ranging from 5 mg to 300 mg CVN058 have been safe and well-tolerated. Daily doses of 25, 75, and 150 mg of CVN058 for 7 days have also been studied, and were similarly safe and well-tolerated.

The timing of dosing was selected to allow the EEG assessments to occur at the corresponding estimated t_{max} values of CVN058. The length of the washout periods is considered adequate based on the PK profile of CVN058.

In addition, based on the EEG deficits reported in subjects with schizophrenia, P50 auditory gating, gamma frequency, and P300 neurophysiological markers will be measured.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety or efficacy of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) / independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization. Subjects who do not initially meet eligibility criteria may be re-screened at investigator's discretion.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is aged 18 to 50 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.
5. The subject meets schizophrenia criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013).
6. The subject is on a stable dose of allowed antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.
7. The subject has a Positive and Negative Syndrome Scale (PANSS) total score of ≤95 at Screening.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* does not agree to use adequate contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.
2. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner does not agree to use acceptable methods of contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

3. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 12 weeks after the last dose of study medication; or intending to donate ova during such time period.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

5. The subject has a history of gastrointestinal disease that would influence the absorption of study drug, or history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).
6. The subject has clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be NCS by the investigator at Screening.
7. The subject has received any investigational compound within 30 days prior to signing of informed consent.
8. The subject has taken any excluded medication or dietary supplement within time frames listed in the Excluded Medications table in Section 7.3.
9. The subject does not have a stable indoor living situation (e.g., living independently, with family, or group home)
10. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
11. Subjects with moderate to severe substance use disorder according to DSM-5 criteria.
12. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use, including marijuana) at Screening.
13. The subject has a history of cancer requiring chemotherapy within the past 5 years prior to the first dose of study medication. This criterion does not include subjects successfully treated for basal cell or stage I squamous cell carcinoma of the skin.
14. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (unless having completed curative therapy), or known history of human immunodeficiency virus (HIV) antibody at Screening.
15. The subject has a QT interval with Fridericia's correction method (QTcF) >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec, confirmed by triplicate testing at 5 minute intervals, at the Screening Visit.
16. The subject has poor peripheral venous access.
17. The subject has hair or scalp condition(s) that would prevent the application of the EEG electrodes.
18. The subject has a current diagnosis of a significant psychiatric illness other than schizophrenia, per DSM-V and is in an acute phase/episode.
19. Subject has clinically meaningful hearing loss per investigator's judgment.
20. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product, within 3 months prior to Day 1.
21. The subject has an abnormal (clinically significant) Screening ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved and documented by signature of the principal investigator (PI).

22. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease, or subject with the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2x the upper limit of normal (ULN).
23. The subject has abnormal Screening vital sign values that suggest a clinically significant underlying disease.
24. The subject has a risk of suicide according to the Investigator's clinical judgment, a Screening Visit Columbia-Suicide Severity Rating Scale [C-SSRS]) score of greater than 3, or has a history of suicide attempt.

7.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a **Prohibited Medications**

28 Days Prior to Check-in	1 Days Prior to Check-in	1 Hour Prior to Each EEG Assessment
Nutraceuticals and dietary supplements (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Alcohol-containing products	Products containing nicotine, caffeine or xanthine (e.g., tea)
Antipsychotic medications, except risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega)	Sedative hypnotic medications (barbiturates and benzodiazepines)	
5-HT_3 receptor antagonists, including ondansetron (Zofran, Zuplenz), granisetron (Kytril, Sancuso, Granisol, Sustol), palonosetron (Aloxi), dolasetron (Anzemet)		
5-HT_3 allosteric modulators buproprion (Wellbutrin, Zyban) and hydroxybupropion		
Serotonin Reuptake Inhibitors (SSRI, SNRI), including sertraline (Zoloft), fluoxetine (Prozac, Sarafem), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle), vortioxetine (Trintellix), and fluvoxamine (Luvox)		
Mirtazapine (Remeron), desipramine, imipramine, trimipramine, reboxetine		

Subjects must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting with the investigator. Subjects must be instructed to not make any changes to their concomitant medications during the course of the study without first consulting with the investigator.

During study participation, subjects will maintain usual dosing schedule of antipsychotic medication(s) and approved concomitant medications. Sedative hypnotics will not be allowed after 10 pm the night prior to testing, and until completion of testing the following day.

7.4 Diet, Fluid, Activity Control

Subjects should have their customary meal before each study visit. The contents of the meal should be summarized on the electronic case report form (eCRF).

During EEG and ERP assessments, subjects will remain still in a seated or partially recumbent position, according to the EEG acquisition guidelines. Subjects will refrain from strenuous exercise from 72 hours before Check-in through check-out, relative to each Treatment Period.

If subject is a smoker; they must refrain from smoking at least 1 hour prior to the EEG testing at all time points.

On each dosing day, CVN058 or placebo will be administered with approximately 240 mL of water.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 ×ULN, or
   – ALT or AST >5 ×ULN and persists for more than 2 weeks, or
   – ALT or AST >3 ×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 ×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post randomization or after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN058 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral solutions, as needed.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN058 and Matching Placebo

CVN058 drug substance is supplied as bulk powder to the clinical site to be compounded into an oral solution. A matching placebo containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor.

CVN058 oral solution will be prepared in concentrations of 10 mg/mL. The composition of the oral solutions (active and placebo) can be found in Table 8.a.

The oral solution will be labeled with the appropriate study information and caution statements.

Table 8.a Composition of CVN058 and Matching Placebo

Component	10 mg/mL solution	Placebo
CVN058 (free base)	10 g	Not Applicable
Citric Acid Monohydrate, USP	15.76 g	15.76 g
Sterile Water for Irrigation, USP	q.s. to 1,000 mL	q.s.to 1,000 mL

q.s.=quantity sufficient, USP= United States Pharmacopeia.

8.1.1.2 Sponsor-Supplied Drug

CVN058 drug substance is supplied to the clinical site by Cerevance by way of a contract manufacturing organization, Johnson-Mathey Pharma Services, Devens, MA.

8.1.1.3 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN058 powdered drug substance is stored at room temperature. CVN058 oral solution and matching placebo can be stored protected from light at 2°C-8°C (35.6°F-46.4°F) for up to 28 days. CVN058 oral solution and matching placebo are stable at room temperature for up to 24 hours.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the PI or designee, who will be blinded to the dose.

Subjects will receive CVN058 (15 mg or 150 mg) or matching placebo in each of the 3 periods.

Table 8.b describes the treatment and medication type that would be provided for each period.

Table 8.b Treatment and Medication Type

Regimen	Planned Treatment	Medication Type
A	Placebo	Placebo
B	CVN058 15 mg	CVN058
C	CVN058 150 mg	CVN058

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

The SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated, e.g., administration of supportive therapy as directed by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract and initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned a 7-digit subject number in the sequential order in which they are randomized beginning with a 3-digit code "NNN-" where NNN represents a site specific identifier which will be provided by the Sponsor. Replacement subjects will be assigned a new number (e.g. site number followed by subject number). The 7-digit subject number assigned will be entered in the subject's eCRF and noted on any subject specific source record and lab sample tubes.

This 7-digit subject number will also be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.

8.3 Randomization Code Creation and Storage

The randomization schedule will be generated under the direction of Cerevance statistician or designee and a copy will be provided to the site pharmacist prior to the start of study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and assignment of causality for AEs should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by contacting the dispensing pharmacist.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

No change should be made to any assessment of the subject after unblinding.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed per site's procedures.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Cerevance must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs CVN058 or placebo on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiration date and amount dispensed, including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site

must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject Screening number will be assigned to each subject at the time that the informed consent is obtained; this Screening number will be used until the subject has been randomized into the study, at which time the Subject number will be primary method of identification on study records.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

The pharmacogenomic sample collection is optional.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, reproductive status (including last menstrual period) and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 45 days (for subjects with schizophrenia) prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the initial Screening physical examination must be assessed by the investigator as not clinically significant (NCS) or clinically significant (CS) and recorded in the source document and eCRF.

Any CS change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

The standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is measured in centimeters, the BMI formula uses meters for height; meters can be determined by dividing centimeters by 100. Thus, for example, if height=176 cm (1.76 m) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818\ kg/m^2$.

Results for BMI will be expressed with 1 decimal place and rounding is allowed. The above value should be captured as 25.6 kg/m^2 in the database.

9.1.5 Vital Sign Procedure

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

Vital signs consisting of body temperature (oral), respiration rate, blood pressure and pulse will be measured in a seated resting state ($\geq$10 minutes).

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Cerevance. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and as stipulated in the Schedule of Study Procedures (Appendix A). Abnormal Screening labs may be

repeated once at the discretion of the investigator for assessment of eligibility. Subjects who still do not meet eligibility criteria may be re-screened at investigator's discretion.

Table 9.a lists the tests that will be obtained for each laboratory specimen

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets Prothrombin time /INR/Partial thromboplastin time (PTT)	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc
Diagnostic Screening:		
Serum	**Urine**	**Saliva (d)**
Serum hCG (a) At Screening Only: Hepatitis panel, including HBsAg and anti-HCV FSH (b)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c)	Alcohol cotinine

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, RBC=red blood cells, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L to obviate the need for contraception.
(c) To be performed at Screening.
(d) Alcohol and cotinine saliva samples may be collected, if needed.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

All laboratory safety data will be transferred electronically to Cerevance or designee in the format requested by Cerevance. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results into the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the PI or sub-investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

During the study and for 12 weeks after last dose of study medication, nonsterilized males and female subjects of childbearing potential who are sexually active must agree to use two effective methods of contraception.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

The following are acceptable forms of contraception:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly).
- Diaphragm (plus spermicidal cream or jelly).

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.

Hormonal Contraception (stable regimen)

- Birth control pills or patch.
- Injected hormonal contraceptive (such as Depo-Provera).
- Vaginal hormonal ring (such as NuvaRing).

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive guidance with respect to the avoidance of pregnancy. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication. Male subjects must be advised not to donate sperm from signing of informed consent to 12 weeks after the last dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects who have only received placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female

partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded in a supine position resting for at least 10 minutes at Screening to assess eligibility. The ECGs will be recorded in triplicate at approximately 5 minute intervals. The investigator (or a qualified physician at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. A copy of the ECG trace should be kept with the subject's notes.

ECGs will be read automatically and also, the investigator or sub-investigator or a suitably qualified delegate will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal NCS, or abnormal and CS. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary.

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.12 Pharmacogenomic Sample Collection

Every subject must sign informed consent/be consented in order to participate in the study, but consent to participate in the pharmacogenomic sample collection (genetic substudy) is optional.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN058.
- Finding out more information about how CVN058 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN058.
- Identifying variations in genes related to the biological target of CVN058.

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN058 and other study medications, and for improving the efficiency, design and study methods of future research studies.

The DNA samples will be used to evaluate common variations in genes which encode drug metabolizing enzymes and transporters. This could be helpful in understanding why there are differences in CVN058 kinetics between subjects. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Whole blood will be collected and stored for possible DNA or RNA isolation and analysis.

DNA sample collection:

> One 6 mL whole blood sample will be collected before study drug dosing on Day 1 of Period 1 only from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K2EDTA) spray-coated tubes, and stored under frozen conditions.

RNA sample collection:

> Two whole blood samples (2.5 mL per sample) will be collected from each subject into a PAXgene tube on Day 1 of each period at pre dose and post EEG for RNA pharmacogenomic analysis.

If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 7-digit subject ID. Detailed instructions for the handling, shipping, and storage of pharmacogenomic samples will be provided in the lab manual.

The samples will be stored for no longer than 15 years after completion of the CVN058 study and/or until the drug development of CVN058 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Cerevance.

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) will be collected for analysis of CVN058, and its metabolite if appropriate; plasma will be collected into chilled vacutainers containing K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment will be provided in the lab manual.

Serial blood samples for determination of CVN058, and its metabolite if appropriate, in plasma will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for CVN058 Pharmacokinetic Analysis

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 15 minutes prior to dosing), 1 hour post dose (pre-EEG), and 5 hours post dose (post-EEG)

The PK samples will be collected before any other assessments are performed, if scheduled at the same time point. The actual time of sample collection will be recorded on the source document and eCRF.

Placebo samples will not be analyzed by the bioanalytical laboratory except 1 sample per subject receiving placebo around the expected time at which CVN058 C_{max} is expected to occur to ensure from a safety perspective that no subjects have inadvertently received active treatment.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of CVN058 will be measured by high-performance liquid chromatography with tandem mass spectrometry. If appropriate, plasma samples analyzed for CVN058 also may be analyzed for the CVN058 metabolite.

9.1.14 Pharmacokinetic Parameters

The PK parameters of CVN058, and its metabolite (if appropriate), will be derived using non-compartmental analysis methods. The PK parameters will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma. Other parameters may be calculated as appropriate.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
C_{max}	Maximum observed plasma concentration.
t_{max}	Time to reach C_{max}.

9.1.15 Pharmacodynamic Sample Collection

MMN will be used as a PD assessment. At each testing session, the following PD assessments will be performed during the EEG: MMN, P50, gamma power, and P300. Collection of P50 may be omitted if the essential equipment is not available. The testing session during each Treatment Period will begin approximately 1.5 hours after administration of study drug.

9.1.16 Pharmacodynamic Parameters

All EEG parameters will be obtained in accordance with the EEG acquisition guideline provided by Cerevance or their designee. It is anticipated that each EEG procedure will take approximately 4 hours to complete, including approximately 30 minutes to set up, 3 hours acquisition time, and 30 minutes to clean up.

MMN

MMN is a pre-attentive auditory component elicited by deviant stimuli in an auditory oddball task. MMN predominantly reflects activation of neuronal ensembles within primary auditory cortex, and thus indexes sensory level disturbance in schizophrenia. MMN will be obtained

independently to pitch and duration deviant stimuli. MMN is maximal at frontocentral electrodes (Fz, Cz). Mean peak amplitude at 5 electrodes surrounding Fz within a predefined latency range will be the primary outcome measure.

P50

P50 auditory evoked potentials will be recorded. Participants will be seated and instructed to relax and to focus their eyes on a fixation point. Stimulus signal of 90-dB pulses of 0.1 msec in duration will be generated and recorded the event-related potential waveforms.
32 pairs of auditory clicks will be presented every 10 seconds, with a 500 msec interclick interval.

The conditioning P50 wave (S1) and test P50 wave (S2) will be identified as the power in the alpha/beta frequency bands as suggested by Smucny et al. (Smucny, 2013). The data from the vertex (Cz) and surrounding electrodes will be collected and the P50 gating ratios will be calculated as the ratio of the test P50 to the conditioning P50 power. In case the Cz gating ratio is >0.2 units above the surrounding electrodes, the value will be discarded and replaced with the value from surrounding electrodes. P50 ratio will be defined as the ratio of S2/S1 power. The S2-S1 difference score as suggested by Smucny et al. (Smucny, 2013) will be used as an exploratory outcome measure.

Quantitative Electroencephalogram, Gamma Power

Five minute eyes open/close recordings will be obtained during each recording session. Ten 1-second, artifact-free epochs will be chosen for quantitative analysis. Primary outcome measures will consist of power within delta (0.5 – 4 Hz), theta (4-7 Hz), alpha (8-13 Hz), delta (13-20 Hz), low gamma (20-40 Hz) and high gamma (40 – 60 Hz) over predesignated frontal, central, temporal and occipital sites. In addition, specific measures of 40 Hz activity will be assessed in response to repetitive 40 Hz auditory stimulation.

P300

As opposed to MMN, which are obtained under passive (i.e., no-task) conditions, auditory P300 will be obtained only when subjects must attend to and detect novel task-relevant deviant stimuli. Generators for P300 are located in distributed frontoparietal networks and so represent an index of higher order, “cognitive” processing in schizophrenia. P300 will be obtained to deviant auditory stimuli in an auditory “oddball” paradigm. P300 is maximal in amplitude at Fz and Pz electrodes. Primary outcome measures will consist of peak amplitude within prespecified latency range at the frontal/parietal sites.

9.1.17 Positive and Negative Syndrome Scale

The PANSS was developed and standardized for typological and dimensional assessment of schizophrenic phenomena. In this study, empirically derived factors are tested excluding those items that could not be assessed during the test sessions: positive symptom factor (delusions, unusual thoughts, somatic concern, grandiosity, suspiciousness, and hallucinations), negative symptom factor (emotional withdrawal, blunted affect, poor rapport, disturbance of volition, preoccupation, and motor retardation), cognitive factor (difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgment and insight, poor attention,

tension, mannerisms, and posturing), hostility (excitement, hostility, impulse control, and uncooperativeness), emotional discomfort (depression, anxiety, and guilt). PANSS will be collected at Screening, Early Termination, and at the Follow-up Visit if clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

The duration of the PANSS is approximately 30 minutes (Kay, 1990).

9.1.18 Columbia Suicide Severity Rating Scale

The determination and management of patients' suicidality risk is the Investigators' responsibility. For study purposes, suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Mundt, 2013).

The C-SSRS is a 2-page questionnaire that prospectively assesses suicidal thoughts and behavior using a structured interview for patient responses. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt).

Different versions of the scale are available. In this study, "Baseline/Screening" version will be used at Screening Visit and "Since last visit" version at all subsequent visits. "Since the last visit" should collect information from the last visit where C-SSRS was administered. If the patient's response generates a change in the findings report from negative to positive, the patient should be referred for immediate psychiatric evaluation on the same date as the site visit. Positive suicidality findings, if confirmed by the PI, is considered to be a serious event. If arising after signing informed consent but prior to administration of any study medication, it is considered a Pretreatment Event (PTE). If arising after administration of any study medication, it is considered an SAE.

The C-SSRS will be administered by the PI or a trained designee on paper and captured in the eCRF. The same interviewer should be used throughout the study for the same subject where possible.

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.

- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail Screening should not be reused.

9.1.20 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. Randomization will take place on Day 1 of Treatment Period 1.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects with schizophrenia will be screened within 28 days prior to enrollment. All subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screen failures. Following written informed consent, Screening procedures may be conducted on different days. Assessments to be conducted during the Screening period are outlined in Appendix A.

9.3.2 Treatment Phase

The treatment will be administered over 3 Periods, separated by 7-10 days for washout. Assessments to be conducted during the screening period are outlined in Appendix A.

9.3.3 Final Visit/End of Treatment

The Final Visit additional assessments will occur prior to Discharge from the clinic at the end of Treatment Period 3, Day 1, as outlined in Appendix A.

For all subjects who received any study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The procedures outlined in Appendix A will be performed and documented.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by telephone approximately 7-10 days after receiving the last dose of study medication (Treatment Period 3) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. The genetic material will be preserved and retained by a biorepository contracted by Cerevance for up to but not longer than 15 years or as required by applicable law.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study. During the "storage" stage, the sample will be used in the analysis of the study drug and related disease states. At this stage, sample and data are linked to personal health information with code numbers. This link means that patients may be identifiable but only indirectly. The code numbers will be kept secure by the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening (x1)	Number of Samples per Period (x 3 Periods)	End of Treatment	Total Volume (mL)
Safety Laboratory Samples (a)	12.5	1	--	1	25
Hepatitis Panel	5	1	--		5
FSH (b)	3	1	--		3
PK Samples	6	--	9	--	54
DNA Sample	6	--	1 (c)	--	6
RNA Samples	5	--	6	--	30
Total Blood Sampling Volume (per Study)					123

(a) Includes Hematology, serum chemistry, and coagulation panel.

(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e. last regular menstrual cycle >2 years) and not surgically sterile.

(c) Only collected in Day 1, Period 1.

The maximum volume of blood at any single day is approximately 40 mL, and the approximate total volume of blood for the study is approximately 123 mL.

Direct venipuncture is the preferred method of blood collection. Any other method will need to be approved by the Sponsor.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.
- Suicidal Ideation and Behavior:
- A completed suicide is always a SAE based on its fatal outcome. C-SSRS score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) would likely indicate serious suicidal ideation and can be used to trigger intervention procedures to provide urgent care. Such procedures may include further evaluation and appropriate management; and/or immediate contact with (or need for a referral to) the subject's mental health practitioner; and/or possible referral to the emergency room; and/or admission to an in-subject unit. For the purpose of this protocol active suicidal ideation level 4 and 5 should be considered important medical events and reported as serious irrespective of whether the subject was hospitalized or not.
- Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or intention to act will be collected as non-serious adverse events in accordance with the standard AE reporting requirements (e.g., if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE).
- A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the eCRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as a serious adverse event.
- Acts of self-mutilation or self-injury without suicidal intention (i.e., self-imposed cigarette burns), will be collected as non-serious adverse events, unless they meet other seriousness criteria.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
   - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Medically Significant AE List (Table 10.a).

Table 10.a Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Serotonin syndrome
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE (e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE).

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.

- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication on Day 1 Period 1 of Part 2 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1 Treatment Period 1. Routine collection of AEs will continue until 21 days following last dose.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the

eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Cerevance SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Cerevance SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report, but becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Cerevance personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principle investigator must review the data change for completeness and accuracy, and must sign, and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the beginning of Part 2. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set

The Safety Set will consist of all subjects who are randomized and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration of CVN058.

Pharmacodynamic Set

The PD Set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the PK and PD endpoint analyses, but data for all subjects will be presented in the subject listings.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by sequence and overall. Summary statistics (number of subjects, mean, median, standard deviation, minimum and maximum) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, ethnicity, race, smoking status, and caffeine consumption).

13.1.3 Pharmacokinetic Analysis

The concentration of CVN058, and its metabolite if appropriate, in plasma will be summarized over each scheduled sampling interval using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

Descriptive statistics will be used to summarize the plasma PK parameters for CVN058, and its metabolite if appropriate. In addition, geometric mean and percent coefficient of variation will be computed for C_{max} and AUC_t.

A more detailed analysis will be presented in the SAP.

13.1.4 Pharmacodynamic Analysis

Observed values for the PD parameters (MMN and exploratory PD parameters) at each time point will summarized by treatment and compared to placebo using summary statistics. Comparison of post dose PD parameters from time-matched placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for time point, sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the LS mean differences between CVN058 and placebo in changes of PD parameters from time-matched period baseline to each postdose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Exposure-response relationships for CVN058 will be explored graphically.

13.1.5 Safety Analysis

The Safety Set will be used for all summaries of TEAEs, laboratory tests, and vital signs. All safety data will be summarized by treatment.

AEs will be presented in listings. TEAEs will be classified according to system organ class and preferred term and will be tabulated with a breakdown by treatment and by event severity. Similar TEAE tabulations will be performed on those events assessed by the investigator as related to study drug.

Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Physical exam findings, suicidality assessments (C-SSRS), and PANSS scores will be presented in data listings.

13.2 Determination of Sample Size

Enrollment of 20 subjects with schizophrenia is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is considered to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. PK samples collected outside of the intervals (listed in Table 14.a), ECGs, vital signs, and RNA pharmacogenomic samples collected outside of the listed intervals are minor deviations and do not require the Protocol Deviation Form to be completed but must be documented in the subject's source documents. A Protocol Deviation eCRF should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

Protocol Deviations should be captured in the site source document for PK samples collected outside of the following intervals:

Table 14.a Windows for Pharmacokinetic Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes predose	Pre-dose (-0.25 hour)
±5	Postdose 1 hour
±15	Postdose 5 hours

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific Screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet

(if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Cerevance will, at a minimum register interventional clinical trials it sponsors on ClinicalTrials.gov or other publicly accessible websites before start of study. Cerevance contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available

for public viewing. For some registries, Cerevance will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject Screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Cerevance providing this information to callers must provide Cerevance with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Cerevance may post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

		CVN058 and Placebo Treatment Periods 1, 2, and 3 (a)		End of Treatment		Follow-up
Study Day:	**Visit 1: Screening**	**Day 1 pre-dose**	**Day 1 post-dose**	**Period 3, End Day 1**	**Early Termination (c)**	**Day 7-10 After End of Treatment (b)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Medication history	X					
Physical examination	X	X		X	X	
Vital signs (d)	X	X	X		X	
Weight, height, and BMI (e)	X			X	X	
Concomitant medications (f)	X	X	X		X	X
Concurrent medical conditions (g)	X					
Clinical laboratory tests (h)	X			X	X	
Hepatitis panel	X					
Audiometric Screening and Tone Matching test (i)	X					
FSH (j)	X					
Pregnancy test (hCG), serum except as noted	X	X (urine)			X	
Urine drug and saliva alcohol screen	X					
ECG	X					
EEG battery (k)			X			
MMN (l)			X			
DNA sample collection (m)		X				
RNA sample collection (n)		X	X			
PK blood collection (o)		X	X		X	
Study drug dosing (p)			X			
PTE assessment (q)	X	X				
AE assessment (r)			X		X	X
C-SSRS (s)	X		X		X	
PANSS (t)	X		X		X	

Footnotes are on last table page.

(a) Minimum 7-day and maximum 10-day washout period is required in between Treatment Periods 1, 2 and 3.
(b) The Follow-up Visit will occur by telephone 7-10 days after End of Treatment unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Conduct procedures for subjects discontinued early per Protocol Section 7.6. The PK sample should be collected at the Early Termination Visit, if within 1 hour of a scheduled PK time point.
(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, and in Periods 1, 2, and 3 (pre dose [within 30 minutes prior to dosing], and at 1 and 5 hours post dose), and at Early Termination (if applicable), and if clinically indicated according to Investigator discretion at the Follow-up visit.
(e) Height and BMI will be collected at Screening only.
(f) Record all patient medications from Screening and throughout the study.
(g) All new concurrent medical conditions arising post-oi should be recorded as PTE or AE.
(h) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening and prior to check-out at End of Treatment or Early Termination, and at the Investigator discretion if a Follow-up Visit is indicated.
(i) Audiometric Screening assessment conducted according to local practice.
(j) A FSH level will be obtained on post menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(k) For the EEG battery, testing will be done at Day 1 starting approximately 1.5 hours post dose for each period and will last approximately 3 hours. NOTE: Subjects should refrain from drinking coffee and smoking approximately 1 hour prior to the EEG assessment until discharge from clinic at the end of the afternoon.
(l) MMN will be the first EEG assessment conducted in the battery.
(m) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to study drug administration on Day 1 of Period 1 only. If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.
(n) Two 2.5 mL whole blood samples will be collected for each Period (Periods 1, 2, and 3) on Day 1 at pre-dose, and 5 hours post- dose
(o) Blood samples (6 mL) for PK analyses will be collected at pre -dose (within 15 minutes prior to dosing), and 1 and 5 hours post dose.
(p) Dosing will only occur on Day 1 of each period, and signals the start of the post-dose Day 1 visit assessments.
(q) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(r) Any adverse event with onset or exacerbation after dosing on Day 1 of Period 1 will be captured as an AE or SAE.
(s) The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered after EEG/ERP collection on each dosing day, and End of Treatment or Early Termination (if applicable).
(t) The Screening/Baseline PANSS will be collected at Screening, approximately 5 hours after each dose (post EEG) and at Early Termination (if applicable).

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form 1572) which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form 1572.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non- standard panel) Screening assessments are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CRF Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

PROTOCOL

A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia

Short title: CVN058 Effect on Mismatch Negativity in Schizophrenics

Sponsor:	Cerevance Alpha (hereafter, "Cerevance") One Marina Park Drive, suite 1410 Boston, MA 02210		
Study Number:	CVN058-103		
IND Number:	121,520	**EudraCT Number:**	N/A
Compound:	CVN058		
Date:	27 Mar 2019	**Amendment Number:**	3
Previous Versions:			
	28 Sep 2018	**Amendment Number:**	2
	02 Jul 2018	**Amendment Number:**	1
	21 May 2018	**Original**	

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	CliniLabs Fax: 919-591-0004 Email: safety@safeharborpv.com
Medical Monitor (carries overall responsibility for the conduct of the study)	[redacted], MD, CPI Director of Medical Affairs, CliniLabs [redacted]
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD PhD Senior Vice President Cerevance, Inc. [redacted]

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Approved by:

Signature [redacted] Date [redacted]

[redacted] MD PhD
Senior Vice President

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in the clinical trial agreement with Cerevance.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance Alpha, Inc. (hereafter referred to as "Cerevance")	**Compound:** CVN058	
Title of Protocol: A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia	**IND No.:** 121,520	**EudraCT No.:** Not Applicable
Study Number: CVN058-103	**Phase:** 1	

Study Design:

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential mismatch negativity (MMN) downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a pharmacodynamic (PD) marker.

Male and female subjects with schizophrenia (including schizoaffective disorder), age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 2.a) to receive 1 of 3 dose regimens in each period: a single oral administration of CVN058 (15 mg or 150 mg) or matching placebo. The sequence will determine the order in which a subject will take each of the 3 regimens. Discontinued subjects may be replaced at the discretion of the sponsor so that approximately 20 completed subjects are available for analysis. Sample size re-estimation may occur when blinded MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study.

The study includes three 1-day treatment periods, with a minimum of 7-day washout, maximum 10-day washout (2 total washouts, after Periods 1 and 2) between periods, and a 7-10 day follow-up call post dosing of the last period. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 2.a Treatment Sequences

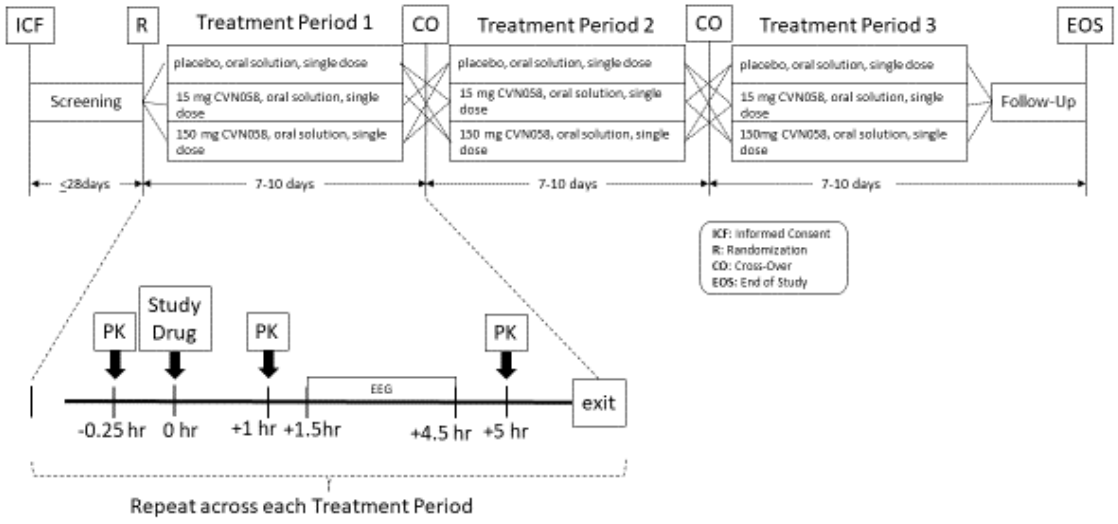
Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects undergo post dose electroencephalography (EEG) testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dosing and at various time points post dose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented below:



Primary Objective:

To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

Secondary Objective:

Assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

Exploratory Objectives:

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

Subject Population:

Subjects with stable schizophrenia including schizoaffective disorder on antipsychotic medication(s).

Number of Subjects:	**Number of Sites:**
Estimated total: at least 20 evaluable subjects who complete the study. Sample size is subject to re-estimation based on blinded preliminary data.	Approximately 3 (United States)
Dose Level(s): Placebo: solution vehicle, oral administration CVN058: 15 mg solution, oral administration CVN058: 150 mg solution, oral administration	**Route of Administration:** Oral
Duration of Treatment: Single oral dose in each of the 3 periods.	**Period of Evaluation:** Screening Days: Up to 28 days. 3 Treatment Periods, each <1 day duration;

	with a 7-10 day washout between periods Follow-up call 7-10 days following the last dose of study drug in Treatment Period 3. Total Duration: Up to 58 days.
Main Criteria for Inclusion: Subjects 18 to 50 years of age, inclusive, at the time of informed consent. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening. Subject meets schizophrenia or schizoaffective disorder criteria as defined by the Diagnostic & Statistical Manual of Mental Disorders, 5th Edition (DSM–V). Subjects are on a stable dose of antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff. Subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95.	
Main Criteria for Exclusion: Subject currently receiving treatment with any excluded medication or dietary supplement. Subjects who have a history of gastrointestinal disease that would influence the absorption of study drug or have a history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection). Subjects having clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be not clinically significant (NCS) by the investigator at Screening. Subjects with moderate to severe substance use disorder, unstable mood or anxiety disorder. Subject has a current diagnosis of a significant psychiatric illness other than schizophrenia or schizoaffective disorder per DSM-V and is in an acute phase/episode. Subject has clinically meaningful hearing loss.	

Main Criteria for Evaluation and Analyses:

Pharmacodynamics:

MMN will be measured as a PD marker for CVN058. Exploratory measurements include P50 auditory gating, gamma power, and P300, which are EEG markers commonly impaired in subjects with schizophrenia including schizoaffective disorder.

Pharmacokinetics:

Blood samples will be collected for the determination of plasma concentrations of CVN058, and its metabolite if appropriate, at the following time points: Pre-dose (within 15 minutes prior to dosing), and at 1 (pre-EEG) and 5 (post-EEG) hours post dose. Analysis of these samples will confirm drug exposure during EEG data collection and will support basic PK/PD response correlations. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the curve from time 0 to 5 hours post dose (AUC_t). Other parameters may be calculated if appropriate.

Pharmacogenomics:

Whole blood will be collected and stored for possible deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolation and analysis.

DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to variability in the PK of CVN058. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Statistical Considerations:

Observed values for the PD parameters (MMN and exploratory PD parameters) in each period will be summarized by treatment and compared to time matched assessments during placebo dosing using summary statistics. Comparison of post dose PD parameters to time matched placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the least squares mean differences between CVN058 and placebo in changes of PD parameters, comparing CVN058 and placebo at a time-matched post-dose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Plasma PK concentrations and parameters of CVN058, and its metabolite if appropriate, will be listed and summarized by treatment using descriptive statistics. Exposure-response relationships for CVN058 will be explored graphically.

Adverse events (AEs) will be presented in listings, and treatment-emergent AEs (TEAEs) will be summarized by treatment. Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Sample size re-estimation will occur after twelve (12) subjects have completed all study visits, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. The sample size re-estimation will be performed using SAS® PROC POWER for Paired-Sample Means and specifications of power = 80%, alpha=0.10 and the blinded group standard deviation values attained from the twelve study subjects.

Sample Size Justification:

Enrollment of 20 subjects is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is expected to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

Sample size re-estimation may occur when blinded MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. Sample size may be increased up to a total of 40 subjects to ensure adequate study power if the lowest MMN values for already studied subjects show less impairment than is expected for a schizophrenic population.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HT_3	5-hydroxytryptamine (serotonin) receptor 3
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from 0 to 5 hours post dose
BA	bioavailability
BMI	body mass index
CIAS	cognitive impairment associated with schizophrenia
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM -V	Diagnostic & Statistical Manual of Mental Disorders, 5th Edition – Text Revision
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalography
EMA	European Medicines Agency
ERP	evoked response potential
FDA	Food and Drug Administration
FM	frequency-modulation
FSH	follicle-stimulating hormone
FSI	fast-spiking interneurons
F_z	frontal electrodes
F_z,C_z	frontocentral electrodes
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	potassium ethylenediamine tetraacetic acid

LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMN	mismatch negativity
NCS	not clinically significant
NMDAR	N-methyl-D-aspartate receptor
NFSI	non-fasting spiking interneurons
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
PTE	pretreatment event
PV	parvalbumin
P_z	parietal electrodes
P50 Ratio	ratio of S2 to S1
RNA	ribonucleic acid
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SSR	steady state response
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
CVN058	also known as ENV8058 and TAK-058
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WHODRUG	World Health Organization Drug Dictionary

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a complex disorder comprising several clinical features that are highly variable among affected individuals. Probably the most well-known schizophrenia symptom domains are the so-called positive symptoms, e.g., hallucinations, delusions, disorganization of thought, bizarre behavior, and incongruity of affect. Negative symptoms include avolition (loss of motivation), blunt affect, alogia (reduced speech), and anhedonia (reduced ability to experience pleasure). Symptoms of a mood disorder, such as mania and depression, are prominent in a subset of patients; those patients are considered to have schizoaffective disorder. There is a well-established cognitive impairment associated with schizophrenia (CIAS) including schizoaffective disorder (Hartman, 2019). CIAS is observed in most cases involving deficits in a broad range of domains.

Cognitive impairment is considered a core feature of schizophrenia and represents an area of significant unmet medical need. Cognitive deficits in schizophrenia include problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green, 2006). These cognitive deficits are believed to underlie much of the significant functional impairments observed in schizophrenia, such as impairment in independent living skills, social functions, vocational functioning, and self-care (Harvey, 2007). Thus, the core nature of CIAS and the associations that have been demonstrated with functional disability suggest that improving cognitive impairment may lead to improved functional outcomes (Heinrichs, 2005).

The understanding of CIAS has evolved significantly in recent years and led to new therapeutic strategies. In postmortem samples from schizophrenic patients, studies consistently reveal reduced levels of enzymes that synthesize the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the prefrontal cortex (McNally, 2013) a key center for higher cognitive function. The GABAergic neurons deficient in the cortex are termed fast-spiking interneurons (FSIs), and they express the marker parvalbumin (PV) (McNally, 2013). These PV+ FSIs are chemically coupled and release GABA in a rhythmic pattern that synchronizes the activity of local cortical pyramidal neurons (Cardin, 2009). This synchronization, which is essential for cognition, is disrupted in patients [(McNally, 2013), (Cardin, 2009)] [(Whittington, 1997), (Rotaru, 2012), (Gonzalez-Burgos, 2012)]. These and other human and animal model data implicate FSI hypofunction, and a resulting imbalance in the excitation/inhibition balance in cortical regions, in CIAS.

Based on this emerging insight into disease pathophysiology, a therapeutic that restores the normal function of the cortical pyramidal neuron/FSI microcircuit would be expected to improve cognitive function in patients with schizophrenia. One strategy for boosting the function of this circuit is to inhibit a second population of inhibitory GABAergic interneurons, known as non-fast spiking interneurons (NFSIs), which project locally onto the FSIs and the dendrites of the pyramidal neurons. These NFSIs are modulated by a wide variety of inputs, particularly excitatory glutamatergic efferents from the thalamus, and noradrenergic, cholinergic, and serotonergic efferents from subcortical regions [(Tian, 2010), (Kawaguchi, 1998), (Kawaguchi, 1997), (Lee, 2010)]. Thus, NFSIs appear to integrate state-dependent information and release GABA to regulate pyramidal neuron/FSI microcircuits.

Mismatch negativity (MMN) is an established biomarker of cortical function (Javitt, 2015). This signal is obtained as an evoked potential during an auditory oddball task, in which a subject is repeatedly exposed to auditory tones and a small proportion of those tones (the "deviant" stimuli) differ from the others (the "standard" stimuli) in their frequency or duration. Typically, the tones are presented and the evoked potentials are recorded while subjects are engaged on a different task, such as reading. Normally, the occurrence of a deviant stimulus increases the amplitude of the negative component in the evoked potential occurring at around 200 msec. MMN is the difference in amplitude between deviant and standard stimuli responses, and is considered to represent an aspect of preattentive novelty detection. MMN is consistently reduced in schizophrenia patients relative to healthy individuals, a finding extensively replicated and with a large effect size (Cohen's $d = 1$). MMN reduction in schizophrenia has been shown to reflect impaired N-methyl-D-aspartate receptor (NMDAR) function at the level of supratemporal auditory cortex, dependent on cortical interneuron modulation of pyramidal cell activity and NMDA receptor-dependent (Lee, 2017).

4.2 Non-Clinical

CVN058 (also known as ENV8058 or TAK-058) is a small molecule that potently and selectively antagonizes the 5-hydroxytryptamine (5-HT) receptor type 3 (5-HT_3). 5-HT_3 is a cys-loop family ligand-gated ion channel that allows cations to pass into the neurons when activated by serotonin, and is highly expressed in NFSIs [(Lee, 2010), (Lummis, 2012)]. The receptor is a pentamer consisting of at least two 5-HT_{3a} subunits and 3 other subunits; in the central nervous system (CNS) the receptor is almost exclusively a homomeric pentamer comprised of 5-HT_{3a} (Kawaguchi, 1997). The 5-HT_3 channel opens when serotonin molecules interact with the 2 ligand recognition sites in the extracellular side of the receptor. Influxed calcium and other positive ions depolarize the NFSIs, leading to GABA release. CVN058 is orally absorbed and readily passes the blood brain barrier, allowing it to occupy cortical 5-HT_3 receptors. CNS 5-HT_3 receptor occupancy is correlated with efficacy in a rat model of cognition where it reverses deficits in novel object recognition induced by subchronic phencyclidine treatment. Thus, CVN058 is a novel therapeutic candidate that may improve cognitive function by inhibiting specific subsets of cortical interneurons.

Additional information from the nonclinical studies can be found in the current Investigator's Brochure.

4.3 Clinical

Two human clinical studies of CVN058 have been completed (ENV8058_101 and TAK-058-1002).

CVN058 was well tolerated up to a dose of 150 mg administered orally as a single dose in aqueous solution (Study ENV8058_101). There were no deaths or other serious adverse events (SAEs) reported in this study and no subject discontinued study due to a treatment-emergent adverse event (TEAE). There were no clinically significant (CS) laboratory abnormalities, electrocardiogram (ECG) changes or changes in vital signs in the completed single dose study.

The mean C_{max} and area under the plasma concentration–time curve (AUC) values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 5 to

150 mg, but mean C_{max} and AUC values increase in an approximately dose proportional manner across the 5 to 45 mg dose range. The rate of appearance of CVN058 in plasma was rapid with median time to C_{max} (t_{max}) values of 1 to 1.25 hours across the dose range of 5 to 150 mg. The mean terminal elimination half-life ($t_{1/2z}$) values of CVN058 ranged from approximately 2.8 to 10.5 hours across the cohorts; the lower doses (5 to 30 mg) had lower mean $t_{1/2z}$ values compared to the higher doses (45 to 150 mg). There were no trends with mean apparent clearance (CL/F) values of CVN058 with increasing dose from 5 to 45 mg, but faster apparent clearance was observed at the 75 and 150 mg doses, possibly due to decreased bioavailability (BA) at higher doses. The mean apparent volume of distribution (V_z/F) increased as dose increased. Excretion of unchanged CVN058 in the urine was ≤2.3% of the administered CVN058 dose over the dose range evaluated.

In the multiple-rising dose study (TAK-058-1002), CVN058 was well-tolerated at daily doses of 25, 75, and 150 mg for 7 days, and at a single 300 mg dose, in aqueous solution. There were no deaths or other SAEs reported in this study and no subject discontinued study due to a TEAE. There were no clinically significant laboratory abnormalities, ECG changes or changes in vital signs in the completed single dose study. Following single or multiple doses, the mean C_{max} and AUC values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 25 to 300 mg. No accumulation was observed following daily administration. CVN058 concentrations in cerebrospinal fluid (CSF) were assessed after daily doses of CVN058 75 mg for 5 days. The CSF concentrations averaged 17.5 ng/mL, or approximately 1% of the concentration in plasma.

4.4 Rationale for the Proposed Study

This study will explore central target engagement and proof of mechanism by measuring auditory evoked potential MMN as a pharmacodynamic (PD) marker of CNS response to the selective 5-HT_3 receptor antagonist CVN058. It has been reported that subjects with schizophrenia including schizoaffective disorder commonly demonstrate a deficit in neural processing that is manifested as a reduction in MMN (Avissar, 2018); impairment of auditory sensory gating (P50) is also observed (Javitt and Sweet, 2015). Other 5-HT_3 receptor antagonists have been reported to improve impairments in auditory evoked potentials in schizophrenic subjects. In a study with ondansetron, a 5-HT_3 receptor antagonist, using P50 auditory gating as the auditory evoked potential measure, subjects were given a single dose of ondansetron (16 mg) or placebo in a double-blind, placebo-controlled, randomized and balanced crossover design (Adler, 2005). Serial measurements of the P50 evoked potential were done at Baseline and 1, 2, and 3 hours after receipt of placebo or ondansetron. The results of the study indicated that ondansetron significantly enhanced P50 auditory gating in subjects with schizophrenia. Tropisetron, a 5-HT_3 antagonist that also has α7 nicotinic cholinergic agonist activity, has similarly been shown to improve P50 auditory gating in subjects with schizophrenia (Koike, 2005).

While the P50 signal is likely a reflection of brainstem and thalamic network activity and is sensitive to antipsychotic treatment, MMN is thought to reflect excitation-inhibition balance in cortical circuits and is not sensitive to antipsychotic treatment (Javitt and Sweet, 2015). Therefore, to evaluate the potential for CVN058 to improve cognitive function in schizophrenics, MMN will be used as a PD marker. The study will be performed as a 3-way crossover to assess

the effect on MMN of CVN058 at two dose levels relative to placebo, with each subject serving as his or her own control to reduce variability. P50 auditory gating will also be measured, as an exploratory endpoint, along with other potentially informative electrophysiological and psychometric parameters.

Medications that might inhibit or mask the effects of CVN058 will not be permitted as concomitant medications. These include serotonin reuptake inhibitors which increase synaptic serotonin levels, as well as drugs that bind to 5-HT_3 at clinically relevant concentrations or are reported to inhibit signaling through 5-HT_3 non-competitively, including some antipsychotic drugs [(Eisensamer, 2005), (Eisensamer, 2003), (Rammes, 2004)]. Permissible antipsychotic medications are risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

5.1.2 Secondary Objective

- To assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

5.1.3 Exploratory Objectives

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

5.2 Endpoints

5.2.1 Primary Endpoints

- Mean amplitude of duration MMN at 5 electrodes surrounding frontal (Fz) electrodes following administration of CVN058 compared to placebo.

5.2.2 Secondary Endpoint

- Percentage of subjects who experience at least 1 TEAE
- Percentage of subjects who experience at least 1 clinically significant abnormal laboratory test result

5.2.3 Exploratory Endpoints

- Mean P50 ratio (S2/S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo
- Mean P50 differences (S2-S1) at 5 electrodes surrounding Cz following administration of CVN058 compared to placebo.
- Pre-stimulus gamma amplitude following administration of CVN058 compared to placebo
- P300 amplitude and latency at average of 5 centroparietal electrodes around parietal electrodes (Pz) following administration of CVN058 compared to placebo

- MMN amplitude to additional deviants (frequency, intensity, location, frequency-modulation [FM]) and latency to all deviants following administration of CVN058 compared to placebo
- CVN058, its metabolite if appropriate, C_{max}, t_{max}, and area under the plasma concentration-time curve from 0 to 5 hours post dose (AUC_t).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential MMN downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a PD marker.

Male and female subjects with schizophrenia including schizoaffective disorder, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 6.a) to receive 1 of 3 dose regimens in each period; a single oral administration of CVN058 (15 mg or 150 mg), or a matching placebo. The sequence will determine the order in which a subject will receive each of the 3 regimens. Discontinued subjects may be replaced so that 20 completed subjects are available for analysis. Sample size re-estimation may occur when blinded MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study.

Each treatment period is less than 1 day in duration, with a minimum of 7-day washout, maximum 10-day washout between doses. A follow-up telephone call will occur approximately 7-10 days following the last dose received. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 6.a Treatment Sequences

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

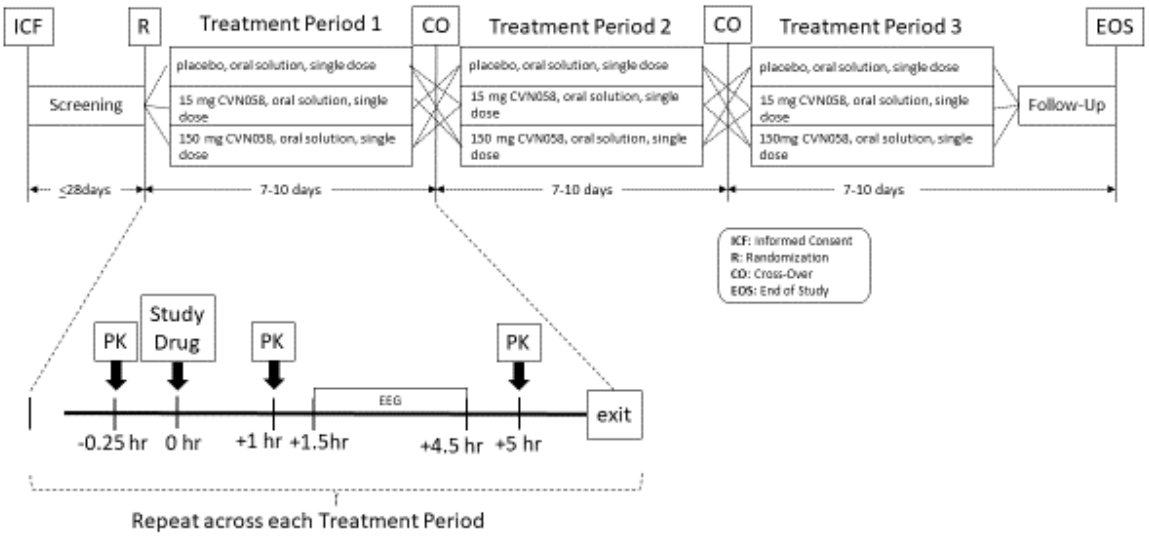
A: Placebo
B: CVN058 15 mg
C: CVN058 150 mg

At each testing session, subjects will undergo post dose EEG testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water in the morning. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dose and at various time points postdose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers. Analysis of these samples will confirm drug exposure during EEG data collection and will support basic PK/PD response correlations.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented in Figure 6.a.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

This study will explore CNS target engagement by measuring alterations in auditory evoked potentials, similar to the demonstration of an effect on P50 auditory gating using the 5-HT_3 antagonist, ondansetron (Adler, 2005). The study design was based on that published study, adapted for CVN058 as study drug and MMN as the primary endpoint. It has been reported that most subjects with schizophrenia demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50). According to Adler et al., ondansetron improves the P50 deficit after a single dose administration (Adler, 2005).

The study will be a randomized, 3 period crossover study (CVN058 at two dose levels, and placebo) in order to evaluate the effect of CVN058 on MMN as well as on exploratory measures (i.e., P50 auditory gating, gamma power, and P300) compared to placebo. The study will be double-blind and placebo-controlled in order to avoid subjective bias in the assessment of the PD markers. In addition, conduct of study procedures for each subject will occur at approximately the same time per day across each of the Treatment Periods to avoid diurnal changes that may otherwise confound the analysis.

The 150 mg level of CVN058 is expected to saturate CNS 5-HT3 receptors throughout the EEG session, but is 50% lower than the highest dosage for which safety and tolerability has been demonstrated in previous phase 1 studies in healthy subjects, thus presumably maximizing the PD signal within the established limits of safe use. The lower dose level of 15 mg CVN058 is expected to attain a lower CNS 5-HT3 receptor occupancy, decreasing to possibly 70-80% by the end of the EEG session. The 10-fold difference in these dosages should help establish a dose-response relationship for evoked response potential (ERP) effects of CVN058. From a safety

perspective, single doses ranging from 5 mg to 300 mg CVN058 have been safe and well-tolerated. Daily doses of 25, 75, and 150 mg of CVN058 for 7 days have also been studied, and were similarly safe and well-tolerated.

The timing of dosing was selected to allow the EEG assessments to occur at the corresponding estimated t_{max} values of CVN058. The length of the washout periods is considered adequate based on the PK profile of CVN058.

In addition, based on the EEG deficits reported in subjects with schizophrenia including schizoaffective disorder, P50 auditory gating, gamma frequency, and P300 neurophysiological markers will be measured.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety or efficacy of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) / independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization. Subjects who do not initially meet eligibility criteria may be re-screened at investigator's discretion.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is aged 18 to 50 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.
5. The subject meets schizophrenia or schizoaffective disorder criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013).
6. The subject is on a stable dose of allowed antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.
7. The subject has a Positive and Negative Syndrome Scale (PANSS) total score of ≤95 at Screening.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* does not agree to use adequate contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.
2. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner does not agree to use acceptable methods of contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

3. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 12 weeks after the last dose of study medication; or intending to donate ova during such time period.

4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a history of gastrointestinal disease that would influence the absorption of study drug, or history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).
6. The subject has clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be NCS by the investigator at Screening.
7. The subject has received any investigational compound within 30 days prior to signing of informed consent.
8. The subject has taken any excluded medication or dietary supplement within time frames listed in the Excluded Medications table in Section 7.3.
9. The subject does not have a stable indoor living situation (e.g., living independently, with family, or group home)
10. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
11. Subjects with moderate to severe substance use disorder according to DSM-5 criteria.
12. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use, including marijuana) at Screening.
13. The subject has a history of cancer requiring chemotherapy within the past 5 years prior to the first dose of study medication. This criterion does not include subjects successfully treated for basal cell or stage I squamous cell carcinoma of the skin.
14. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (unless having completed curative therapy), or known history of human immunodeficiency virus (HIV) antibody at Screening.
15. The subject has a QT interval with Fridericia's correction method (QTcF) >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec, confirmed by triplicate testing at 5-minute intervals, at the Screening Visit.
16. The subject has poor peripheral venous access.
17. The subject has hair or scalp condition(s) that would prevent the application of the EEG electrodes.
18. The subject has a current diagnosis of a significant psychiatric illness other than schizophrenia or schizoaffective disorder, per DSM-V and is in an acute phase/episode.
19. Subject has clinically meaningful hearing loss per investigator's judgment.
20. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product, within 3 months prior to Day 1.

21. The subject has an abnormal (clinically significant) Screening ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved and documented by signature of the principal investigator (PI).
22. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease, or subject with the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2x the upper limit of normal (ULN).
23. The subject has abnormal Screening vital sign values that suggest a clinically significant underlying disease.
24. The subject has a risk of suicide according to the Investigator's clinical judgment, a Screening Visit Columbia-Suicide Severity Rating Scale [C-SSRS]) score of greater than 3, or has a history of suicide attempt in the past 3 years.

7.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a **Prohibited Medications**

28 Days Prior to Check-in	1 Days Prior to Check-in	1 Hour Prior to Each EEG Assessment
Nutraceuticals and dietary supplements (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Alcohol-containing products	Products containing nicotine, caffeine or xanthine (e.g., tea)
Antipsychotic medications, except risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify) and paliperidone (Invega)	Sedative hypnotic medications (barbiturates and benzodiazepines)	
5-HT_3 receptor antagonists, including ondansetron (Zofran, Zuplenz), granisetron (Kytril, Sancuso, Granisol, Sustol), palonosetron (Aloxi), dolasetron (Anzemet)		
5-HT_3 allosteric modulators buproprion (Wellbutrin, Zyban) and hydroxybupropion		
Serotonin Reuptake Inhibitors (SSRI, SNRI), including sertraline (Zoloft), fluoxetine (Prozac, Sarafem), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle), vortioxetine (Trintellix), and fluvoxamine (Luvox)		
Mirtazapine (Remeron), desipramine, imipramine, trimipramine, reboxetine		

Subjects must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting with the investigator. Subjects must be instructed to not make

any changes to their concomitant medications during the course of the study without first consulting with the investigator.

During study participation, subjects will maintain usual dosing schedule of antipsychotic medication(s) and approved concomitant medications. Sedative hypnotics will not be allowed after 10 pm the night prior to testing, and until completion of testing the following day.

7.4 Diet, Fluid, Activity Control

Subjects should have their customary meal before each study visit. The contents of the meal should be summarized on the electronic case report form (eCRF).

During EEG and ERP assessments, subjects will remain still in a seated or partially recumbent position, according to the EEG acquisition guidelines. Subjects will refrain from strenuous exercise from 72 hours before Check-in through check-out, relative to each Treatment Period.

If subject is a smoker; they must refrain from smoking at least 1 hour prior to the EEG testing at all time points.

On each dosing day, CVN058 or placebo will be administered with approximately 240 mL of water.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 ×ULN, or
   – ALT or AST >5 ×ULN and persists for more than 2 weeks, or
   – ALT or AST >3 ×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 ×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post randomization or after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN058 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral solutions, as needed.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN058 and Matching Placebo

CVN058 drug substance is supplied as bulk powder to the clinical site to be compounded into an oral solution. A matching placebo containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor.

CVN058 oral solution will be prepared in concentrations of 10 mg/mL. The composition of the oral solutions (active and placebo) can be found in Table 8.a.

The oral solution will be labeled with the appropriate study information and caution statements.

Table 8.a Composition of CVN058 and Matching Placebo

Component	10 mg/mL solution	Placebo
CVN058 (free base)	10 g	Not Applicable
Citric Acid Monohydrate, USP	15.76 g	15.76 g
Sterile Water for Irrigation, USP	q.s. to 1,000 mL	q.s.to 1,000 mL

q.s.=quantity sufficient, USP= United States Pharmacopeia.

8.1.1.2 Sponsor-Supplied Drug

CVN058 drug substance is supplied to the clinical site by Cerevance by way of a contract manufacturing organization, Johnson-Matthey Pharma Services, Devens, MA.

8.1.1.3 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN058 powdered drug substance is stored at room temperature. CVN058 oral solution and matching placebo can be stored protected from light at 2°C-8°C (35.6°F-46.4°F) for up to 28 days. CVN058 oral solution and matching placebo are stable at room temperature for up to 24 hours.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the PI or designee, who will be blinded to the dose.

Subjects will receive CVN058 (15 mg or 150 mg) or matching placebo in each of the 3 periods.

Table 8.b describes the treatment and medication type that would be provided for each period.

Table 8.b Treatment and Medication Type

Regimen	Planned Treatment	Medication Type
A	Placebo	Placebo
B	CVN058 15 mg	CVN058
C	CVN058 150 mg	CVN058

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

The SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated, e.g., administration of supportive therapy as directed by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract and initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned a 7-digit subject number in the sequential order in which they are randomized beginning with a 3-digit code "NNN-" where NNN represents a site-specific identifier which will be provided by the Sponsor. Replacement subjects will be assigned a new number (e.g. site number followed by subject number). The 7-digit subject number assigned will be entered in the subject's eCRF and noted on any subject specific source record and lab sample tubes.

This 7-digit subject number will also be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.

8.3 Randomization Code Creation and Storage

The randomization schedule will be generated under the direction of Cerevance statistician or designee and a copy will be provided to the site pharmacist prior to the start of study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and assignment of causality for AEs should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by contacting the dispensing pharmacist.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

No change should be made to any prior assessments or data of the subject after unblinding.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed per site's procedures.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Cerevance must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs CVN058 or placebo on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiration date and amount dispensed, including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site

must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject Screening number will be assigned to each subject at the time that the informed consent is obtained; this Screening number will be used until the subject has been randomized into the study, at which time the Subject number will be primary method of identification on study records.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

The pharmacogenomic sample collection is optional.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, reproductive status (including last menstrual period) and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 45 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the initial Screening physical examination must be assessed by the investigator as not clinically significant (NCS) or clinically significant (CS) and recorded in the source document and eCRF.

Any CS change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

The standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is measured in centimeters, the BMI formula uses meters for height; meters can be determined by dividing centimeters by 100. Thus, for example, if height=176 cm (1.76 m) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818\ kg/m^2$.

Results for BMI will be expressed with 1 decimal place and rounding is allowed. The above value should be captured as 25.6 kg/m^2 in the database.

9.1.5 Vital Sign Procedure

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw. Vital signs assessments will be collected with a window of ±15 minutes.

Vital signs consisting of body temperature (oral), respiration rate, blood pressure and pulse will be measured in a seated resting state ($\geq$10 minutes).

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Cerevance. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and as stipulated in the Schedule of Study Procedures (Appendix A). Abnormal Screening labs may be repeated once at the discretion of the investigator for assessment of eligibility. Subjects who still do not meet eligibility criteria may be re-screened at investigator's discretion.

Table 9.a lists the tests that will be obtained for each laboratory specimen. Additional laboratory assessments may be performed at the Investigator's discretion and entered in the database for Randomized Subjects only, if the results are deemed Clinically Significant by Investigator.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets Prothrombin time /INR/Partial thromboplastin time (PTT)	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc

Diagnostic Screening:		
Serum	**Urine**	**Saliva (d)**
Serum hCG (a) At Screening Only: Hepatitis panel, including HBsAg and anti-HCV FSH (b)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c)	Alcohol cotinine

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, RBC=red blood cells, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L to obviate the need for contraception.
(c) To be performed at Screening.
(d) Alcohol and cotinine saliva samples may be collected, if needed.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

All laboratory safety data will be transferred electronically to Cerevance or designee in the format requested by Cerevance. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results into the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the PI or sub-investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

During the study and for 12 weeks after last dose of study medication, nonsterilized males and female subjects of childbearing potential who are sexually active must agree to use two effective methods of contraception.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

The following are acceptable forms of contraception:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly).
- Diaphragm (plus spermicidal cream or jelly).

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.

Hormonal Contraception (stable regimen)

- Birth control pills or patch.
- Injected hormonal contraceptive (such as Depo-Provera).
- Vaginal hormonal ring (such as NuvaRing).

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive guidance with respect to the avoidance of pregnancy. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication. Male subjects must be advised not to donate sperm from signing of informed consent to 12 weeks after the last dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects who have only received placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded in a supine position resting for at least 10 minutes at Screening to assess eligibility. The ECGs will be recorded in triplicate at approximately 5-minute intervals, with a window of ±2 minutes. The investigator (or a qualified physician at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. A copy of the ECG trace should be kept with the subject's notes.

ECGs will be read automatically and also, the investigator or sub-investigator or a suitably qualified delegate will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal NCS, or abnormal and CS. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary.

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.12 Pharmacogenomic Sample Collection

Every subject must sign informed consent/be consented in order to participate in the study, but consent to participate in the pharmacogenomic sample collection (genetic substudy) is optional.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN058.
- Finding out more information about how CVN058 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN058.
- Identifying variations in genes related to the biological target of CVN058.

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN058 and other study medications, and for improving the efficiency, design and study methods of future research studies.

The DNA samples will be used to evaluate common variations in genes which encode drug metabolizing enzymes and transporters. This could be helpful in understanding why there are differences in CVN058 kinetics between subjects. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Whole blood will be collected and stored for possible DNA or RNA isolation and analysis.

DNA sample collection:

> One 6 mL whole blood sample will be collected before study drug dosing on Day 1 of Period 1 only from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K2EDTA) spray-coated tubes, and stored under frozen conditions.

RNA sample collection:

> Two whole blood samples (2.5 mL per sample) will be collected from each subject into a PAXgene tube on Day 1 of each period at pre-dose and post EEG for RNA pharmacogenomic analysis.

If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 7-digit subject ID. Detailed instructions for the handling, shipping, and storage of pharmacogenomic samples will be provided in the lab manual.

The samples will be stored for no longer than 15 years after completion of the CVN058 study and/or until the drug development of CVN058 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Cerevance.

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) will be collected for analysis of CVN058, and its metabolite if appropriate; plasma will be collected into chilled vacutainers containing

K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment will be provided in the lab manual.

Serial blood samples for determination of CVN058, and its metabolite if appropriate, in plasma will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for CVN058 Pharmacokinetic Analysis

Sample Type	Dosing Day	Time Post-dose (hours)
Plasma	1	Pre-dose (within 15 minutes prior to dosing), 1 hour post dose (pre-EEG), and 5 hours post dose (post-EEG)

The PK samples will be collected before any other assessments are performed, if scheduled at the same time point. The actual time of sample collection will be recorded on the source document and eCRF.

Placebo samples will not be analyzed by the bioanalytical laboratory except 1 sample per subject receiving placebo around the expected time at which CVN058 C_{max} is expected to occur to ensure from a safety perspective that no subjects have inadvertently received active treatment.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of CVN058 will be measured by high-performance liquid chromatography with tandem mass spectrometry. If appropriate, plasma samples analyzed for CVN058 also may be analyzed for the CVN058 metabolite.

9.1.14 Pharmacokinetic Parameters

The PK parameters of CVN058, and its metabolite (if appropriate), will be derived using non-compartmental analysis methods. The PK parameters will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma. Other parameters may be calculated as appropriate.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from time 0 to 5 hours post dose.
C_{max}	Maximum observed plasma concentration.
t_{max}	Time to reach C_{max}.

9.1.15 Pharmacodynamic Sample Collection

MMN will be used as a PD assessment. At each testing session, the following PD assessments will be performed during the EEG: MMN, P50, gamma power, and P300. Collection of P50 may be omitted if the essential equipment is not available. The testing session during each Treatment Period will begin approximately 1.5 hours after administration of study drug.

9.1.16 Pharmacodynamic Parameters

All EEG parameters will be obtained in accordance with the EEG acquisition guideline provided by Cerevance or their designee. It is anticipated that each EEG procedure will take approximately 4 hours to complete, including approximately 30 minutes to set up, 3 hours acquisition time, and 30 minutes to clean up.

MMN

MMN is a pre-attentive auditory component elicited by deviant stimuli in an auditory oddball task. MMN predominantly reflects activation of neuronal ensembles within primary auditory cortex, and thus indexes sensory level disturbance in schizophrenia. MMN will be obtained independently to pitch and duration deviant stimuli. MMN is maximal at frontocentral electrodes (Fz, Cz). Mean peak amplitude at 5 electrodes surrounding Fz within a predefined latency range will be the primary outcome measure.

P50

P50 auditory evoked potentials will be recorded. Participants will be seated and instructed to relax and to focus their eyes on a fixation point. Stimulus signal of 90-dB pulses of 0.1 msec in duration will be generated and recorded the event-related potential waveforms.
32 pairs of auditory clicks will be presented every 10 seconds, with a 500 msec interclick interval.

The conditioning P50 wave (S1) and test P50 wave (S2) will be identified as the power in the alpha/beta frequency bands as suggested by Smucny et al. (Smucny, 2013). The data from the vertex (Cz) and surrounding electrodes will be collected and the P50 gating ratios will be calculated as the ratio of the test P50 to the conditioning P50 power. In case the Cz gating ratio is >0.2 units above the surrounding electrodes, the value will be discarded and replaced with the value from surrounding electrodes. P50 ratio will be defined as the ratio of S2/S1 power. The S2-S1 difference score as suggested by Smucny et al. (Smucny, 2013) will be used as an exploratory outcome measure.

Quantitative Electroencephalogram, Gamma Power

Five-minute eyes open/close recordings will be obtained during each recording session. Ten 1-second, artifact-free epochs will be chosen for quantitative analysis. Primary outcome measures will consist of power within delta (0.5 – 4 Hz), theta (4-7 Hz), alpha (8-13 Hz), delta (13-20 Hz), low gamma (20-40 Hz) and high gamma (40 – 60 Hz) over predesignated frontal, central, temporal and occipital sites. In addition, specific measures of 40 Hz activity will be assessed in response to repetitive 40 Hz auditory stimulation.

P300

As opposed to MMN, which are obtained under passive (i.e., no-task) conditions, auditory P300 will be obtained only when subjects must attend to and detect novel task-relevant deviant stimuli. Generators for P300 are located in distributed frontoparietal networks and so represent an index of higher order, “cognitive” processing in schizophrenia. P300 will be obtained to deviant auditory stimuli in an auditory “oddball” paradigm. P300 is maximal in amplitude at Fz and Pz

electrodes. Primary outcome measures will consist of peak amplitude within prespecified latency range at the frontal/parietal sites.

9.1.17 Positive and Negative Syndrome Scale

The PANSS was developed and standardized for typological and dimensional assessment of schizophrenic phenomena. In this study, empirically derived factors are tested excluding those items that could not be assessed during the test sessions: positive symptom factor (delusions, unusual thoughts, somatic concern, grandiosity, suspiciousness, and hallucinations), negative symptom factor (emotional withdrawal, blunted affect, poor rapport, disturbance of volition, preoccupation, and motor retardation), cognitive factor (difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgment and insight, poor attention, tension, mannerisms, and posturing), hostility (excitement, hostility, impulse control, and uncooperativeness), emotional discomfort (depression, anxiety, and guilt). PANSS will be collected at Screening, Early Termination, and at the Follow-up Visit if clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

The duration of the PANSS is approximately 30 minutes (Kay, 1990).

9.1.18 Columbia Suicide Severity Rating Scale

The determination and management of subjects' suicidality risk is the Investigators' responsibility. For study purposes, suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Mundt, 2013).

The C-SSRS is a 2-page questionnaire that prospectively assesses suicidal thoughts and behavior using a structured interview for patient responses. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt).

Different versions of the scale are available. In this study, "Baseline/Screening" version will be used at Screening Visit and "Since last visit" version at all subsequent visits. "Since the last visit" should collect information from the last visit where C-SSRS was administered. If the patient's response generates a change in the findings report from negative to positive, the patient should be referred for immediate psychiatric evaluation on the same date as the site visit. Positive suicidality findings, if confirmed by the PI, is considered to be a serious event. If arising after signing informed consent but prior to administration of any study medication, it is considered a Pretreatment Event (PTE). If arising after administration of any study medication, it is considered an SAE.

The C-SSRS will be administered by the PI or a trained designee on paper and captured in the eCRF. The same interviewer should be used throughout the study for the same subject where possible.

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail Screening should not be reused.

9.1.20 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. Randomization will take place on Day 1 of Treatment Period 1.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects with schizophrenia including schizoaffective disorder will be screened within 28 days prior to enrollment. All subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screen failures. Following written informed consent, Screening procedures may be conducted on different days. Assessments to be conducted during the Screening period are outlined in Appendix A.

9.3.2 Treatment Phase

The treatment will be administered over 3 Periods, separated by 7-10 days for washout. Assessments to be conducted during the screening period are outlined in Appendix A.

9.3.3 Final Visit/End of Treatment

The Final Visit additional assessments will occur prior to Discharge from the clinic at the end of Treatment Period 3, Day 1, as outlined in Appendix A.

For all subjects who received any study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The procedures outlined in Appendix A will be performed and documented.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by telephone approximately 7-10 days after receiving the last dose of study medication (Treatment Period 3) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. The genetic material will be preserved and retained by a biorepository contracted by Cerevance for up to but not longer than 15 years or as required by applicable law.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study. During the "storage" stage, the sample will be used in the analysis of the study drug and related disease states. At this stage, sample and data are linked to personal health information with code numbers. This link means that subjects may be identifiable but only indirectly. The code numbers will be kept secure by the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening (x1)	Number of Samples per Period (x 3 Periods)	End of Treatment	Total Volume (mL)
Safety Laboratory Samples (a)	12.5	1	--	1	25
Hepatitis Panel	5	1	--		5
FSH (b)	3	1	--		3
PK Samples	6	--	9	--	54
DNA Sample	6	--	1 (c)	--	6
RNA Samples	5	--	6	--	30
Total Blood Sampling Volume (per Study)					123

(a) Includes Hematology, serum chemistry, and coagulation panel.

(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e. last regular menstrual cycle >2 years) and not surgically sterile.

(c) Only collected in Day 1, Period 1.

The maximum volume of blood at any single day is approximately 40 mL, and the approximate total volume of blood for the study is approximately 123 mL.

Direct venipuncture is the preferred method of blood collection. Any other method will need to be approved by the Sponsor.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.
- Suicidal Ideation and Behavior:
- A completed suicide is always a SAE based on its fatal outcome. C-SSRS score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) would likely indicate serious suicidal ideation and can be used to trigger intervention procedures to provide urgent care. Such procedures may include further evaluation and appropriate management; and/or immediate contact with (or need for a referral to) the subject's mental health practitioner; and/or possible referral to the emergency room; and/or admission to an in-subject unit. For the purpose of this protocol active suicidal ideation level 4 and 5 should be considered important medical events and reported as serious irrespective of whether the subject was hospitalized or not.
- Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or intention to act will be collected as non-serious adverse events in accordance with the standard AE reporting requirements (e.g., if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE).
- A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the eCRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as a serious adverse event.
- Acts of self-mutilation or self-injury without suicidal intention (i.e., self-imposed cigarette burns), will be collected as non-serious adverse events, unless they meet other seriousness criteria.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
   - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Medically Significant AE List (Table 10.a).

Table 10.a Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Serotonin syndrome
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE (e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE).

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.

- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication on Day 1 Period 1 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1 Treatment Period 1. Routine collection of AEs will continue until 21 days following last dose.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the

eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Cerevance SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Cerevance SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report, but becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Cerevance personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principle investigator must review the data change for completeness and accuracy, and must sign, and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to interim analysis and database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Included in the SAP will be details for a blinded interim analysis and a sample size re-assessment.

A targeted data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set

The Safety Set will consist of all subjects who are randomized and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration of CVN058.

Pharmacodynamic Set

The PD Set will consist of all subjects who receive study drug and have at least 1 post-dose PD measurement.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the PK and PD endpoint analyses, but data for all subjects will be presented in the subject listings.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by sequence and overall. Summary statistics (number of subjects, mean, median, standard deviation, minimum and maximum) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, ethnicity, race, smoking status, and caffeine consumption).

13.1.3 Pharmacokinetic Analysis

The concentration of CVN058, and its metabolite if appropriate, in plasma will be summarized over each scheduled sampling interval using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

Descriptive statistics will be used to summarize the plasma PK parameters for CVN058, and its metabolite if appropriate. In addition, geometric mean and percent coefficient of variation will be computed for C_{max} and AUC_t.

A more detailed analysis will be presented in the SAP.

13.1.4 Pharmacodynamic Analysis

Observed values for the PD parameters (MMN and exploratory PD parameters) will be summarized by treatment and compared to placebo using summary statistics. Comparison of post-dose PD parameters from a time-matched placebo period timepoint will be analyzed using analysis of covariance (ANCOVA) with factors for sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the LS mean of observed differences in PD parameters, comparing CVN058 and placebo at a time-matched post-dose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Exposure-response relationships for CVN058 will be explored graphically.

13.1.5 Safety Analysis

The Safety Set will be used for all summaries of TEAEs, laboratory tests, and vital signs. All safety data will be summarized by treatment.

AEs will be presented in listings. TEAEs will be classified according to system organ class and preferred term and will be tabulated with a breakdown by treatment and by event severity. Similar TEAE tabulations will be performed on those events assessed by the investigator as related to study drug.

Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Physical exam findings, suicidality assessments (C-SSRS), and PANSS scores will be presented in data listings.

Baseline values will be the latest observation prior to dosing in the first study period. Thus, for most assessments, the Baseline value will be the Day 1 pre-dose observation; for Clinical Laboratory assessments, the Baseline values will be from the Screening Visit (Day -28).

13.2 Determination of Sample Size

Enrollment of 20 subjects with schizophrenia is estimated to provide approximately 80% power to detect a mean effect size of Cohen's d=0.5 with an error rate of alpha=0.10. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is considered to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

Sample size re-estimation may occur when blinded MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. To ensure adequate study power, sample size may be increased based on this re-estimation procedure. Further details will be included in the SAP.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. PK samples collected outside of the intervals (listed in Table 14.a), ECGs, vital signs, and RNA pharmacogenomic samples collected outside of the listed intervals are minor deviations and do not require the Protocol Deviation Form to be completed but must be documented in the subject's source documents. A Protocol Deviation eCRF should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

Protocol Deviations should be captured in the site source document for PK samples collected outside of the following intervals:

Table 14.a Windows for Pharmacokinetic Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes predose	Pre-dose (-0.25 hour)
±5	Postdose 1 hour
±15	Postdose 5 hours

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific Screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet

(if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Cerevance will, at a minimum register interventional clinical trials it sponsors on ClinicalTrials.gov or other publicly accessible websites before start of study. Cerevance contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available

for public viewing. For some registries, Cerevance will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject Screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Cerevance providing this information to callers must provide Cerevance with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Cerevance may post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

		CVN058 and Placebo Treatment Periods 1, 2, and 3 (a)		End of Treatment		Follow-up
Study Day:	**Visit 1: Screening**	**Day 1 pre-dose**	**Day 1 post-dose**	**Period 3, End Day 1**	**Early Termination (c)**	**Day 7-10 After End of Treatment (b)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Reproductive Status	X					
Social History	X					
Medication history	X					
Physical examination	X	X		X	X	
Vital signs (d)	X	X	X		X	
Weight, height, and BMI (e)	X			X	X	
Concomitant medications (f)	X	X	X		X	X
Medical history (g)	X					
Clinical laboratory tests (h)	X			X	X	
Hepatitis panel	X					
Audiometric Screening and Tone Matching test (i)	X					
FSH (j)	X					
Pregnancy test (hCG), serum except as noted	X	X (urine)			X	
Urine drug and saliva alcohol screen	X					
ECG (k)	X					
EEG battery (l)			X			
MMN (m)			X			
DNA sample collection (n)		X				
RNA sample collection (o)		X	X			
PK blood collection (p)		X	X		X	
Study drug dosing (q)			X			
PTE assessment (r)	X	X				
AE assessment (s)			X		X	X
C-SSRS (t)	X		X		X	
PANSS (u)	X		X		X	

Footnotes are on last table page.

(a) Minimum 7-day and maximum 10-day washout period is required in between Treatment Periods 1, 2 and 3.
(b) The Follow-up Visit will occur by telephone 7-10 days after End of Treatment unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Conduct procedures for subjects discontinued early per Protocol Section 7.6. The PK sample should be collected at the Early Termination Visit, if within 1 hour of a scheduled PK time point.
(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, and in Periods 1, 2, and 3 (pre dose [within 30 minutes prior to dosing], and at 1 and 5 hours post dose), and at Early Termination (if applicable), and if clinically indicated according to Investigator discretion at the Follow-up visit. Vital signs will be collected with a window of ±15 minutes.
(e) Height and BMI will be collected at Screening only.
(f) Record all patient medications from Screening and throughout the study.
(g) All new medical history arising after signing ICF should be recorded as PTE or AE.
(h) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening and prior to check-out at End of Treatment or Early Termination, and at the Investigator discretion if a Follow-up Visit is indicated.
(i) Audiometric Screening assessment conducted according to local practice.
(j) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(k) ECGs will be collected with a window of ±2 minutes.
(l) For the EEG battery, testing will be done at Day 1 starting approximately 1.5 hours post dose for each period and will last approximately 3 hours. NOTE: Subjects should refrain from drinking coffee and smoking approximately 1 hour prior to the EEG assessment until discharge from clinic at the end of the afternoon.
(m) MMN will be the first EEG assessment conducted in the battery. EEG (MMN) assessment will be collected with a window of ±60 minutes.
(n) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to study drug administration on Day 1 of Period 1 only. If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.
(o) Two 2.5 mL whole blood samples will be collected for each Period (Periods 1, 2, and 3) on Day 1 at pre-dose, and 5 hours post- dose
(p) Blood samples (6 mL) for PK analyses will be collected at pre -dose (within 15 minutes prior to dosing), and 1 and 5 hours post dose. PK collection for pre-dose will be (within 15 minutes prior to dosing), ±15 minutes at the 1 hour post-dose time point, and ±30 minutes at the 5 hour post-dose time point.
(q) Dosing will only occur on Day 1 of each period, and signals the start of the post-dose Day 1 visit assessments.
(r) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(s) Any adverse event with onset or exacerbation after dosing on Day 1 of Period 1 will be captured as an AE or SAE.
(t) The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered after EEG/ERP collection on each dosing day, and End of Treatment or Early Termination (if applicable).
(u) The Screening/Baseline PANSS will be collected at Screening, approximately 5 hours after each dose (post EEG) and at Early Termination (if applicable). PANSS will be collected with a window of ±45 minutes.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form 1572) which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form 1572.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non- standard panel) Screening assessments are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CRF Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

PROTOCOL

A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia

Short title: CVN058 Effect on Mismatch Negativity in Schizophrenics

Sponsor:	Cerevance Alpha (hereafter, "Cerevance") One Marina Park Drive, suite 1410 Boston, MA 02210		
Study Number:	CVN058-103		
IND Number:	121,520	**EudraCT Number:**	N/A
Compound:	CVN058		
Date:	24 Sep 2019	**Amendment Number:**	4
Previous Versions:			
	27 Mar 2019	**Amendment Number:**	3
	28 Sep 2018	**Amendment Number:**	2
	02 Jul 2018	**Amendment Number:**	1
	21 May 2018	**Original**	

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	[redacted]
Medical Monitor (carries overall responsibility for the conduct of the study)	[redacted], MD, CPI Director of Medical Affairs, CliniLabs [redacted]
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD PhD Senior Vice President Cerevance, Inc. [redacted]

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Approved by:

Signature [redacted] Date [redacted]

[redacted], MD PhD

Senior Vice President

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in the clinical trial agreement with Cerevance.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance Alpha, Inc. (hereafter referred to as "Cerevance")	**Compound:** CVN058	
Title of Protocol: A Placebo-Controlled Study to Evaluate the Effect of a Single Dose of CVN058 on Mismatch Negativity in Subjects with Stable Schizophrenia	**IND No.:** 121,520	**EudraCT No.:** Not Applicable
Study Number: CVN058-103	**Phase:** 1	

Study Design:

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential mismatch negativity (MMN) downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a pharmacodynamic (PD) marker.

Male and female subjects with schizophrenia (including schizoaffective disorder), age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 2.a) to receive 1 of 3 dose regimens in each period: a single oral administration of CVN058 (15 mg or 150 mg initially; one or both dosages may be revised after interim analysis) or matching placebo. The sequence will determine the order in which a subject will take each of the 3 regimens. Discontinued subjects may be replaced at the discretion of the sponsor so that approximately 20 completed subjects are available for analysis. Sample size re-estimation may occur when MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study.

The study includes three 1-day treatment periods, with a minimum of 7-day washout, maximum 10-day washout (2 total washouts, after Periods 1 and 2) between periods, and a 7-10 day follow-up call post dosing of the last period. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 2.a Treatment Sequences

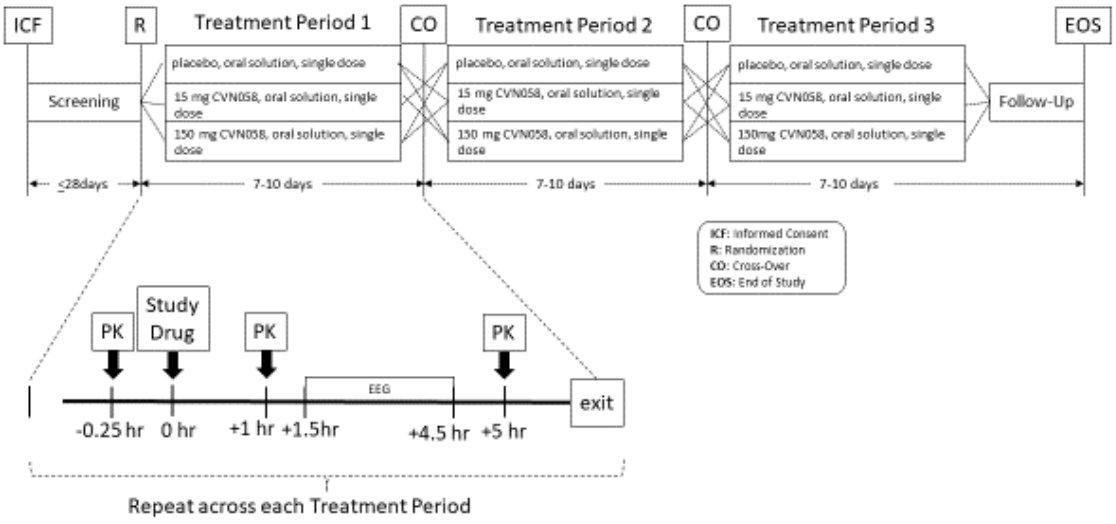
Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

A: Placebo
B: CVN058 15 mg initially; dosage may be revised after interim analysis
C: CVN058 150 mg initially; dosage may be revised after interim analysis

At each testing session, subjects undergo post dose electroencephalography (EEG) testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dosing and at various time points post dose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented below:



Note: CVN058 dosages will be 15 mg and 150 mg initially; one or both dosages may be revised after interim analysis.

Primary Objective:

To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

Secondary Objective:

Assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

Exploratory Objectives:

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- To assess the pharmacokinetics (PK) of CVN058 following a single dose to subjects with schizophrenia.
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

Subject Population:

Subjects with stable schizophrenia including schizoaffective disorder on antipsychotic medication(s).

Number of Subjects:	**Number of Sites:**
Estimated total: at least 20 evaluable subjects who complete the study. Sample size is subject to re-estimation based on preliminary data from an interim analysis.	Approximately 3 (United States)

Dose Level(s):	**Route of Administration:**
Placebo: solution vehicle, oral administration CVN058: 15 mg solution, oral administration CVN058: 150 mg solution, oral administration The CVN058 dosages above will be used from study start; one or both dosages may be revised after interim analysis.	Oral
Duration of Treatment: Single oral dose in each of the 3 periods.	**Period of Evaluation:** Screening Days: Up to 28 days. 3 Treatment Periods, each <1 day duration; with a 7-10 day washout between periods Follow-up call 7-10 days following the last dose of study drug in Treatment Period 3. Total Duration: Up to 58 days.
Main Criteria for Inclusion: Subjects 18 to 50 years of age, inclusive, at the time of informed consent. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening. Subject meets schizophrenia or schizoaffective disorder criteria as defined by the Diagnostic & Statistical Manual of Mental Disorders, 5th Edition (DSM–V). Subjects are on a stable dose of antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff. Subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95.	
Main Criteria for Exclusion: Subject currently receiving treatment with any excluded medication or dietary supplement. Subjects who have a history of gastrointestinal disease that would influence the absorption of study drug or have a history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection). Subjects having clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be not clinically significant (NCS) by the investigator at Screening. Subjects with moderate to severe substance use disorder, unstable mood or anxiety disorder. Subject has a current diagnosis of a significant psychiatric illness other than schizophrenia or schizoaffective disorder per DSM-V and is in an acute phase/episode. Subject has clinically meaningful hearing loss.	

Main Criteria for Evaluation and Analyses:

Pharmacodynamics:

MMN will be measured as a PD marker for CVN058. Exploratory measurements include P50 auditory gating, gamma power, and P300, which are EEG markers commonly impaired in subjects with schizophrenia including schizoaffective disorder.

Pharmacokinetics:

Blood samples will be collected for the determination of plasma concentrations of CVN058, and its metabolite if appropriate, at the following time points: Pre-dose (within 15 minutes prior to dosing), and at 1 (pre-EEG) and 5 (post-EEG) hours post dose. Analysis of these samples will confirm drug exposure during EEG data collection and will support basic PK/PD response correlations. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the curve from time 0 to 5 hours post dose (AUC_t). Other parameters may be calculated if appropriate.

Pharmacogenomics:

Whole blood will be collected and stored for possible deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolation and analysis.

DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to variability in the PK of CVN058. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Statistical Considerations:

Observed values for the PD parameters (MMN and exploratory PD parameters) in each period will be summarized by treatment and compared to time matched assessments during placebo dosing using summary statistics. Comparison of post dose PD parameters to time matched placebo period timepoints will be analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and factors for sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the least squares mean differences between CVN058 and placebo in changes of PD parameters, comparing CVN058 and placebo at a time-matched post-dose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Plasma PK concentrations and parameters of CVN058, and its metabolite if appropriate, will be listed and summarized by treatment using descriptive statistics. Exposure-response relationships for CVN058 will be explored graphically.

Adverse events (AEs) will be presented in listings, and treatment-emergent AEs (TEAEs) will be summarized by treatment. Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Sample size re-estimation will occur after twelve (12) subjects have completed all study visits, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. The sample size re-estimation will be performed using SAS® PROC POWER for Paired-Sample Means and specifications of power = 80%, alpha=0.10 and the unblinded group standard deviation values attained from the twelve study subjects.

Sample Size Justification:

Enrollment of 20 subjects is estimated to provide >80% power to detect a median effect size of Cohen's d=0.5. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is expected to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

Sample size re-estimation may occur when MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. Sample size may be increased up to a total of 40 subjects to ensure adequate study power to achieve its scientific objectives.

3.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HT_3	5-hydroxytryptamine (serotonin) receptor 3
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from 0 to 5 hours post dose
BA	bioavailability
BMI	body mass index
CIAS	cognitive impairment associated with schizophrenia
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM -V	Diagnostic & Statistical Manual of Mental Disorders, 5th Edition – Text Revision
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalography
EMA	European Medicines Agency
ERP	evoked response potential
FDA	Food and Drug Administration
FM	frequency-modulation
FSH	follicle-stimulating hormone
FSI	fast-spiking interneurons
F_z	frontal electrodes
F_z,C_z	frontocentral electrodes
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	potassium ethylenediamine tetraacetic acid

LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMN	mismatch negativity
NCS	not clinically significant
NMDAR	N-methyl-D-aspartate receptor
NFSI	non-fasting spiking interneurons
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
PTE	pretreatment event
PV	parvalbumin
P_z	parietal electrodes
P50 Ratio	ratio of S2 to S1
RNA	ribonucleic acid
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SSR	steady state response
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
CVN058	also known as ENV8058 and TAK-058
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WHODRUG	World Health Organization Drug Dictionary

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a complex disorder comprising several clinical features that are highly variable among affected individuals. Probably the most well-known schizophrenia symptom domains are the so-called positive symptoms, e.g., hallucinations, delusions, disorganization of thought, bizarre behavior, and incongruity of affect. Negative symptoms include avolition (loss of motivation), blunt affect, alogia (reduced speech), and anhedonia (reduced ability to experience pleasure). Symptoms of a mood disorder, such as mania and depression, are prominent in a subset of patients; those patients are considered to have schizoaffective disorder. There is a well-established cognitive impairment associated with schizophrenia (CIAS) including schizoaffective disorder (Hartman, 2019). CIAS is observed in most cases involving deficits in a broad range of domains.

Cognitive impairment is considered a core feature of schizophrenia and represents an area of significant unmet medical need. Cognitive deficits in schizophrenia include problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green, 2006). These cognitive deficits are believed to underlie much of the significant functional impairments observed in schizophrenia, such as impairment in independent living skills, social functions, vocational functioning, and self-care (Harvey, 2007). Thus, the core nature of CIAS and the associations that have been demonstrated with functional disability suggest that improving cognitive impairment may lead to improved functional outcomes (Heinrichs, 2005).

The understanding of CIAS has evolved significantly in recent years and led to new therapeutic strategies. In postmortem samples from schizophrenic patients, studies consistently reveal reduced levels of enzymes that synthesize the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the prefrontal cortex (McNally, 2013) a key center for higher cognitive function. The GABAergic neurons deficient in the cortex are termed fast-spiking interneurons (FSIs), and they express the marker parvalbumin (PV) (McNally, 2013). These PV+ FSIs are chemically coupled and release GABA in a rhythmic pattern that synchronizes the activity of local cortical pyramidal neurons (Cardin, 2009). This synchronization, which is essential for cognition, is disrupted in patients [(McNally, 2013), (Cardin, 2009)] [(Whittington, 1997), (Rotaru, 2012), (Gonzalez-Burgos, 2012)]. These and other human and animal model data implicate FSI hypofunction, and a resulting imbalance in the excitation/inhibition balance in cortical regions, in CIAS.

Based on this emerging insight into disease pathophysiology, a therapeutic that restores the normal function of the cortical pyramidal neuron/FSI microcircuit would be expected to improve cognitive function in patients with schizophrenia. One strategy for boosting the function of this circuit is to inhibit a second population of inhibitory GABAergic interneurons, known as non-fast spiking interneurons (NFSIs), which project locally onto the FSIs and the dendrites of the pyramidal neurons. These NFSIs are modulated by a wide variety of inputs, particularly excitatory glutamatergic efferents from the thalamus, and noradrenergic, cholinergic, and serotonergic efferents from subcortical regions [(Tian, 2010), (Kawaguchi, 1998), (Kawaguchi, 1997), (Lee, 2010)]. Thus, NFSIs appear to integrate state-dependent information and release GABA to regulate pyramidal neuron/FSI microcircuits.

Mismatch negativity (MMN) is an established biomarker of cortical function (Javitt, 2015). This signal is obtained as an evoked potential during an auditory oddball task, in which a subject is repeatedly exposed to auditory tones and a small proportion of those tones (the "deviant" stimuli) differ from the others (the "standard" stimuli) in their frequency or duration. Typically, the tones are presented and the evoked potentials are recorded while subjects are engaged on a different task, such as reading. Normally, the occurrence of a deviant stimulus increases the amplitude of the negative component in the evoked potential occurring at around 200 msec. MMN is the difference in amplitude between deviant and standard stimuli responses, and is considered to represent an aspect of preattentive novelty detection. MMN is consistently reduced in schizophrenia patients relative to healthy individuals, a finding extensively replicated and with a large effect size (Cohen's $d = 1$). MMN reduction in schizophrenia has been shown to reflect impaired N-methyl-D-aspartate receptor (NMDAR) function at the level of supratemporal auditory cortex, dependent on cortical interneuron modulation of pyramidal cell activity and NMDA receptor-dependent (Lee, 2017).

4.2 Non-Clinical

CVN058 (also known as ENV8058 or TAK-058) is a small molecule that potently and selectively antagonizes the 5-hydroxytryptamine (5-HT) receptor type 3 (5-HT_3). 5-HT_3 is a cys-loop family ligand-gated ion channel that allows cations to pass into the neurons when activated by serotonin, and is highly expressed in NFSIs [(Lee, 2010), (Lummis, 2012)]. The receptor is a pentamer consisting of at least two 5-HT_{3a} subunits and 3 other subunits; in the central nervous system (CNS) the receptor is almost exclusively a homomeric pentamer comprised of 5-HT_{3a} (Kawaguchi, 1997). The 5-HT_3 channel opens when serotonin molecules interact with the 2 ligand recognition sites in the extracellular side of the receptor. Influxed calcium and other positive ions depolarize the NFSIs, leading to GABA release. CVN058 is orally absorbed and readily passes the blood brain barrier, allowing it to occupy cortical 5-HT_3 receptors. CNS 5-HT_3 receptor occupancy is correlated with efficacy in a rat model of cognition where it reverses deficits in novel object recognition induced by subchronic phencyclidine treatment. Thus, CVN058 is a novel therapeutic candidate that may improve cognitive function by inhibiting specific subsets of cortical interneurons.

Additional information from the nonclinical studies can be found in the current Investigator's Brochure.

4.3 Clinical

Two human clinical studies of CVN058 have been completed (ENV8058_101 and TAK-058-1002).

CVN058 was well tolerated up to a dose of 150 mg administered orally as a single dose in aqueous solution (Study ENV8058_101). There were no deaths or other serious adverse events (SAEs) reported in this study and no subject discontinued study due to a treatment-emergent adverse event (TEAE). There were no clinically significant (CS) laboratory abnormalities, electrocardiogram (ECG) changes or changes in vital signs in the completed single dose study.

The mean C_{max} and area under the plasma concentration–time curve (AUC) values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 5 to

150 mg, but mean C_{max} and AUC values increase in an approximately dose proportional manner across the 5 to 45 mg dose range. The rate of appearance of CVN058 in plasma was rapid with median time to C_{max} (t_{max}) values of 1 to 1.25 hours across the dose range of 5 to 150 mg. The mean terminal elimination half-life ($t_{1/2z}$) values of CVN058 ranged from approximately 2.8 to 10.5 hours across the cohorts; the lower doses (5 to 30 mg) had lower mean $t_{1/2z}$ values compared to the higher doses (45 to 150 mg). There were no trends with mean apparent clearance (CL/F) values of CVN058 with increasing dose from 5 to 45 mg, but faster apparent clearance was observed at the 75 and 150 mg doses, possibly due to decreased bioavailability (BA) at higher doses. The mean apparent volume of distribution (V_z/F) increased as dose increased. Excretion of unchanged CVN058 in the urine was ≤2.3% of the administered CVN058 dose over the dose range evaluated.

In the multiple-rising dose study (TAK-058-1002), CVN058 was well-tolerated at daily doses of 25, 75, and 150 mg for 7 days, and at a single 300 mg dose, in aqueous solution. There were no deaths or other SAEs reported in this study and no subject discontinued study due to a TEAE. There were no clinically significant laboratory abnormalities, ECG changes or changes in vital signs in the completed single dose study. Following single or multiple doses, the mean C_{max} and AUC values of CVN058 increased less than proportionally with increasing CVN058 dose across the dose range of 25 to 300 mg. No accumulation was observed following daily administration. CVN058 concentrations in cerebrospinal fluid (CSF) were assessed after daily doses of CVN058 75 mg for 5 days. The CSF concentrations averaged 17.5 ng/mL, or approximately 1% of the concentration in plasma.

4.4 Rationale for the Proposed Study

This study will explore central target engagement and proof of mechanism by measuring auditory evoked potential MMN as a pharmacodynamic (PD) marker of CNS response to the selective 5-HT_3 receptor antagonist CVN058. It has been reported that subjects with schizophrenia including schizoaffective disorder commonly demonstrate a deficit in neural processing that is manifested as a reduction in MMN (Avissar, 2018); impairment of auditory sensory gating (P50) is also observed (Javitt and Sweet, 2015). Other 5-HT_3 receptor antagonists have been reported to improve impairments in auditory evoked potentials in schizophrenic subjects. In a study with ondansetron, a 5-HT_3 receptor antagonist, using P50 auditory gating as the auditory evoked potential measure, subjects were given a single dose of ondansetron (16 mg) or placebo in a double-blind, placebo-controlled, randomized and balanced crossover design (Adler, 2005). Serial measurements of the P50 evoked potential were done at Baseline and 1, 2, and 3 hours after receipt of placebo or ondansetron. The results of the study indicated that ondansetron significantly enhanced P50 auditory gating in subjects with schizophrenia. Tropisetron, a 5-HT_3 antagonist that also has α7 nicotinic cholinergic agonist activity, has similarly been shown to improve P50 auditory gating in subjects with schizophrenia (Koike, 2005).

While the P50 signal is likely a reflection of brainstem and thalamic network activity and is sensitive to antipsychotic treatment, MMN is thought to reflect excitation-inhibition balance in cortical circuits and is not sensitive to antipsychotic treatment (Javitt and Sweet, 2015). Therefore, to evaluate the potential for CVN058 to improve cognitive function in schizophrenics, MMN will be used as a PD marker. The study will be performed as a 3-way crossover to assess

the effect on MMN of CVN058 at two dose levels relative to placebo, with each subject serving as his or her own control to reduce variability. P50 auditory gating will also be measured, as an exploratory endpoint, along with other potentially informative electrophysiological and psychometric parameters.

Medications that might inhibit or mask the effects of CVN058 will not be permitted as concomitant medications. These include serotonin reuptake inhibitors which increase synaptic serotonin levels, as well as drugs that bind to 5-HT_3 at clinically relevant concentrations or are reported to inhibit signaling through 5-HT_3 non-competitively, including some antipsychotic drugs [(Eisensamer, 2005), (Eisensamer, 2003), (Rammes, 2004)]. Permissible antipsychotic medications are risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify), paliperidone (Invega), lurasidone (Latuda), and ziprasidone (Geodon).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To determine whether improvement in MMN is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.

5.1.2 Secondary Objective

- To assess the safety and tolerability of single doses of CVN058 in subjects with schizophrenia.

5.1.3 Exploratory Objectives

- To determine whether improvement in P50 auditory gating, gamma power, and P300 is demonstrated after administration of CVN058 compared to placebo in subjects with schizophrenia.
- [redacted]
- To explore the exposure-response relationship for CVN058 in subjects with schizophrenia.

5.2 Endpoints

5.2.1 Primary Endpoints

- Mean amplitude of duration MMN at 5 electrodes surrounding frontal (Fz) electrodes following administration of CVN058 compared to placebo.

5.2.2 Secondary Endpoint

- Percentage of subjects who experience at least 1 TEAE
- Percentage of subjects who experience at least 1 clinically significant abnormal laboratory test result

5.2.3 Exploratory Endpoints

- [redacted]
- [redacted]
- Pre-stimulus gamma amplitude following administration of CVN058 compared to placebo
- P300 amplitude and latency at average [redacted] following administration of CVN058 compared to placebo

- MMN amplitude to additional deviants (frequency, intensity, location, frequency-modulation [FM]) and latency to all deviants following administration of CVN058 compared to placebo
- [redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, double-blind, placebo-controlled, 3 period cross-over study to evaluate CVN058 target engagement by measuring auditory evoked potential MMN downstream to 5-hydroxytryptamine receptor 3 (5-HT_3) as a PD marker.

Male and female subjects with schizophrenia including schizoaffective disorder, age 18 to 50 years old, inclusive, will be randomized to 1 of 6 treatment sequences (Table 6.a) to receive 1 of 3 dose regimens in each period; a single oral administration of CVN058 (15 mg or 150 mg initially; one or both dosages may be revised after interim analysis), or a matching placebo. The sequence will determine the order in which a subject will receive each of the 3 regimens. Discontinued subjects may be replaced so that 20 completed subjects are available for analysis. Sample size re-estimation may occur when MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study.

Each treatment period is less than 1 day in duration, with a minimum of 7-day washout, maximum 10-day washout between doses. A follow-up telephone call will occur approximately 7-10 days following the last dose received. Subjects may be inpatients or outpatients at the discretion of the Investigator.

Table 6.a Treatment Sequences

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

A: Placebo

B: CVN058 15 mg initially; dosage may be revised after interim analysis

C: CVN058 150 mg initially; dosage may be revised after interim analysis

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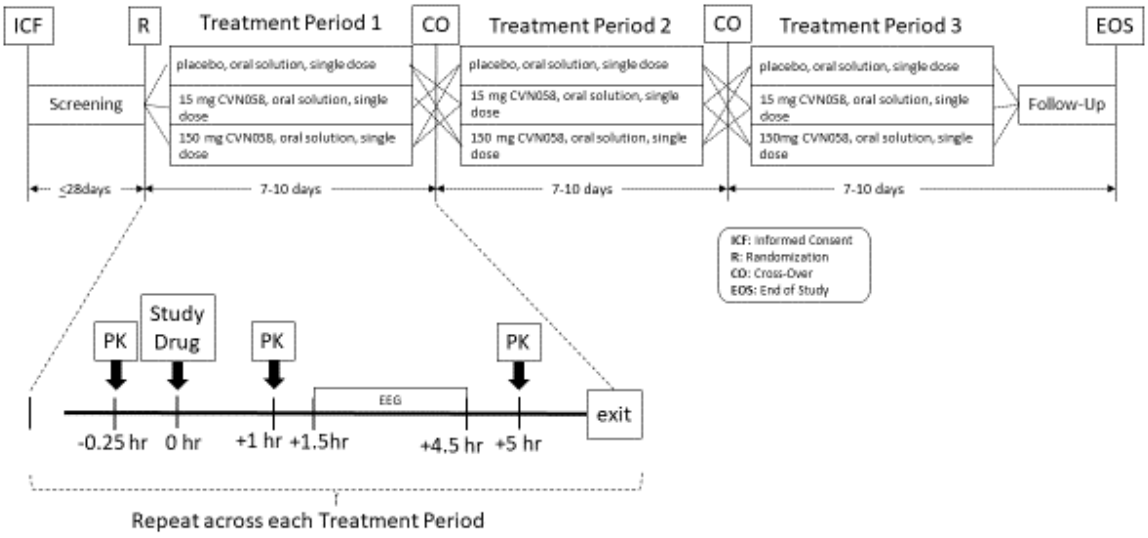
At each testing session, subjects will undergo post dose EEG testing including: MMN, P50, gamma power, and P300. Study drug will be administered with water in the morning. Testing sessions will begin approximately 1.5 hours post-dose. Prior to dose and at various time points post-dose, blood samples will be collected for the assessment of plasma concentrations of CVN058 and biomarkers. Analysis of these samples will confirm drug exposure during EEG data collection and will support basic PK/PD response correlations.

Study procedures will be conducted at approximately the same times across Treatment Periods to minimize diurnal effects on outcomes. The effect of CVN058 on MMN as well as on exploratory measures (e.g., P50 auditory gating, gamma power, and P300) will be compared to placebo.

A schematic of the study design is presented in Figure 6.a.

Figure 6.a Schematic of Study Design



Note: CVN058 dosages will be 15 mg and 150 mg initially; one or both dosages may be revised after interim analysis.

6.2 Justification for Study Design, Dose, and Endpoints

This study will explore CNS target engagement by measuring alterations in auditory evoked potentials, similar to the demonstration of an effect on P50 auditory gating using the 5-HT_3 antagonist, ondansetron (Adler, 2005). The study design was based on that published study, adapted for CVN058 as study drug and MMN as the primary endpoint. It has been reported that most subjects with schizophrenia demonstrate a deficit in neural processing that is manifested as a reduction in MMN and impairment of auditory sensory gating (P50). According to Adler et al., ondansetron improves the P50 deficit after a single dose administration (Adler, 2005).

The study will be a randomized, 3 period crossover study (CVN058 at two dose levels, and placebo) in order to evaluate the effect of CVN058 on MMN as well as on exploratory measures (i.e., P50 auditory gating, gamma power, and P300) compared to placebo. The study will be double-blind and placebo-controlled in order to avoid subjective bias in the assessment of the PD markers. In addition, conduct of study procedures for each subject will occur at approximately the same time per day across each of the Treatment Periods to avoid diurnal changes that may otherwise confound the analysis.

The 150 mg level of CVN058 is expected to saturate CNS 5-HT3 receptors throughout the EEG session, but is 50% lower than the highest dosage for which safety and tolerability has been demonstrated in previous phase 1 studies in healthy subjects, thus presumably maximizing the

PD signal within the established limits of safe use. The lower dose level of 15 mg CVN058 is expected to attain a lower CNS 5-HT3 receptor occupancy, decreasing to possibly 70-80% by the end of the EEG session. The 10-fold difference in these dosages should help establish a dose-response relationship for evoked response potential (ERP) effects of CVN058. From a safety perspective, single doses ranging from 5 mg to 300 mg CVN058 have been safe and well-tolerated. Daily doses of 25, 75, and 150 mg of CVN058 for 7 days have also been studied and were similarly safe and well-tolerated. Following interim analysis, one or both CVN058 dosages may be revised, but will not exceed 150 mg.

The timing of dosing was selected to allow the EEG assessments to occur at the corresponding estimated t_{max} values of CVN058. The length of the washout periods is considered adequate based on the PK profile of CVN058.

In addition, based on the EEG deficits reported in subjects with schizophrenia including schizoaffective disorder, P50 auditory gating, gamma frequency, and P300 neurophysiological markers will be measured.

6.2.1 Dose Modification

The dosages chosen at study outset, 15 mg and 150 mg, span a 10-fold range, with a large gap in between. If unblinded interim data suggest that either dosage is ineffective or poorly tolerated, the Sponsor may elect to discontinue use of that dosage and to replace it with another. The new dosage will not exceed 150 mg.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety or efficacy of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) / independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization. Subjects who do not initially meet eligibility criteria may be re-screened at investigator's discretion.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is aged 18 to 50 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) between 18 and 40 kg/m^2 inclusive at Screening.
5. The subject meets schizophrenia or schizoaffective disorder criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013).
6. The subject is on a stable dose of allowed antipsychotic medication(s) for at least 2 months prior to Screening as documented by medical history and assessed by site staff.
7. The subject has a Positive and Negative Syndrome Scale (PANSS) total score of $\leq$95 at Screening.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* does not agree to use adequate contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.
2. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner does not agree to use acceptable methods of contraception* from signing of informed consent throughout the duration of the study and for 12 weeks after last dose of study drug.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

3. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 12 weeks after the last dose of study medication; or intending to donate ova during such time period.

4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a history of gastrointestinal disease that would influence the absorption of study drug, or history of any surgical intervention known to impact absorption (e.g., bariatric surgery or bowel resection).
6. The subject has clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) outside the reference range for the testing laboratory, unless the results are deemed to be NCS by the investigator at Screening.
7. The subject has received any investigational compound within 30 days prior to signing of informed consent.
8. The subject has taken any excluded medication or dietary supplement within time frames listed in the Excluded Medications table in Section 7.3.
9. The subject does not have a stable indoor living situation (e.g., living independently, with family, or group home)
10. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
11. Subjects with moderate to severe substance use disorder according to DSM-5 criteria.
12. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use, except marijuana) at Screening.
13. The subject has a history of cancer requiring chemotherapy within the past 5 years prior to the first dose of study medication. This criterion does not include subjects successfully treated for basal cell or stage I squamous cell carcinoma of the skin.
14. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (unless having completed curative therapy), or known history of human immunodeficiency virus (HIV) antibody at Screening.
15. The subject has a QT interval with Fridericia's correction method (QTcF) >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec, confirmed by triplicate testing at 5-minute intervals, at the Screening Visit.
16. The subject has poor peripheral venous access.
17. The subject has hair or scalp condition(s) that would prevent the application of the EEG electrodes.
18. The subject has a current diagnosis of a significant psychiatric illness other than schizophrenia or schizoaffective disorder, per DSM-V and is in an acute phase/episode.
19. Subject has clinically meaningful hearing loss per investigator's judgment.
20. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product, within 3 months prior to Day 1.

21. The subject has an abnormal (clinically significant) Screening ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved and documented by signature of the principal investigator (PI).
22. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease, or subject with the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2x the upper limit of normal (ULN).
23. The subject has abnormal Screening vital sign values that suggest a clinically significant underlying disease.
24. The subject has a risk of suicide according to the Investigator's clinical judgment, a Screening Visit Columbia-Suicide Severity Rating Scale [C-SSRS]) score of greater than 3, or has a history of suicide attempt in the past 3 years.

7.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a Prohibited Medications

28 Days Prior to Check-in	1 Days Prior to Check-in	1 Hour Prior to Each EEG Assessment
Nutraceuticals and dietary supplements (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Alcohol-containing products	Products containing nicotine, caffeine or xanthine (e.g., tea)
Antipsychotic medications, except risperidone (Risperdal), haloperidol (Haldol), quetiapine (Seroquel), aripiprazole (Abilify), paliperidone (Invega), lurasidone (Latuda), and ziprasidone (Geodon)	Sedative hypnotic medications (barbiturates and benzodiazepines)	
5-HT_3 receptor antagonists, including ondansetron (Zofran, Zuplenz), granisetron (Kytril, Sancuso, Granisol, Sustol), palonosetron (Aloxi), dolasetron (Anzemet)		
5-HT_3 allosteric modulators buproprion (Wellbutrin, Zyban) and hydroxybupropion		
Serotonin Reuptake Inhibitors (SSRI, SNRI), including sertraline (Zoloft), fluoxetine (Prozac, Sarafem), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle), vortioxetine (Trintellix), and fluvoxamine (Luvox)		
Mirtazapine (Remeron), desipramine, imipramine, trimipramine, reboxetine		

Subjects must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting with the investigator. Subjects must be instructed to not make any changes to their concomitant medications during the course of the study without first consulting with the investigator.

During study participation, subjects will maintain usual dosing schedule of antipsychotic medication(s) and approved concomitant medications. Sedative hypnotics will not be allowed after 10 pm the night prior to testing, and until completion of testing the following day.

7.4 Diet, Fluid, Activity Control

Subjects should have their customary meal before each study visit. The contents of the meal should be summarized on the electronic case report form (eCRF).

During EEG and ERP assessments, subjects will remain still in a seated or partially recumbent position, according to the EEG acquisition guidelines. Subjects will refrain from strenuous exercise from 72 hours before Check-in through check-out, relative to each Treatment Period.

If subject is a smoker; they must refrain from smoking at least 1 hour prior to the EEG testing at all time points.

On each dosing day, CVN058 or placebo will be administered with approximately 240 mL of water.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 ×ULN, or
   – ALT or AST >5 ×ULN and persists for more than 2 weeks, or
   – ALT or AST >3 ×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 ×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post randomization or after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to

protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN058 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral solutions, as needed.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN058 and Matching Placebo

CVN058 drug substance is supplied as bulk powder to the clinical site to be compounded into an oral solution. A matching placebo containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor.

CVN058 oral solution will be prepared in concentrations of 10 mg/mL. The composition of the oral solutions (active and placebo) can be found in Table 8.a.

The oral solution will be labeled with the appropriate study information and caution statements.

Table 8.a Composition of CVN058 and Matching Placebo

Component	10 mg/mL solution	Placebo
CVN058 (free base)	10 g	Not Applicable
Citric Acid Monohydrate, USP	15.76 g	15.76 g
Sterile Water for Irrigation, USP	q.s. to 1,000 mL	q.s.to 1,000 mL

q.s.=quantity sufficient, USP= United States Pharmacopeia.

8.1.1.2 Sponsor-Supplied Drug

CVN058 drug substance is supplied to the clinical site by Cerevance by way of a contract manufacturing organization, Johnson-Matthey Pharma Services, Devens, MA.

8.1.1.3 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN058 powdered drug substance is stored at room temperature. CVN058 oral solution and matching placebo can be stored protected from light at 2°C-8°C (35.6°F-46.4°F) for up to 28 days. CVN058 oral solution and matching placebo are stable at room temperature for up to 24 hours.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the PI or designee, who will be blinded to the dose.

Subjects will be randomized to 1 of 6 treatment sequences (Table 6.a) to receive 1 of 3 dose regimens in each period.

Table 8.b describes the treatment and medication type that would be provided for each period.

Table 8.b Treatment and Medication Type

Regimen	Planned Treatment	Medication Type
A	Placebo	Placebo
B	CVN058 15 mg initially; dosage may be revised after interim analysis	CVN058
C	CVN058 150 mg initially; dosage may be revised after interim analysis	CVN058

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

The SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated, e.g., administration of supportive therapy as directed by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract and initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned a 7-digit subject number in the sequential order in which they are randomized beginning with a 3-digit code "NNN-" where NNN represents a site-specific identifier which will be provided by the Sponsor. Replacement subjects will be assigned a new number (e.g. site number followed by subject number). The 7-digit subject number assigned will be entered in the subject's eCRF and noted on any subject specific source record and lab sample tubes.

This 7-digit subject number will also be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.

8.3 Randomization Code Creation and Storage

The randomization schedule will be generated under the direction of Cerevance statistician or designee and a copy will be provided to the site pharmacist prior to the start of study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and assignment of causality for AEs should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by contacting the dispensing pharmacist.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

Having completed a blinded interim analysis of data for the first 12 completed subjects, the Sponsor has determined that those data will be unblinded per a change to the study plan introduced in Protocol Amendment 4. All data from subsequently enrolled subjects will remain blinded until the study is concluded.

No change should be made to any prior assessments or data of any subject after unblinding of his/her treatment assignment.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed per site's procedures.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Cerevance must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs CVN058 or placebo on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiration date and amount dispensed, including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will

retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject Screening number will be assigned to each subject at the time that the informed consent is obtained; this Screening number will be used until the subject has been randomized into the study, at which time the Subject number will be primary method of identification on study records.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

The pharmacogenomic sample collection is optional.

9.1.2 Demographics, Medical History, Medication History Procedure, Reproductive Status

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, and smoking status of the subject at Screening.

Reproductive status will be collected including last menstrual period.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 45 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the initial Screening physical examination must be assessed by the investigator as not clinically significant (NCS) or clinically significant (CS) and recorded in the source document and eCRF.

Any CS change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

The standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is measured in centimeters, the BMI formula uses meters for height; meters can be determined by dividing centimeters by 100. Thus, for example, if height=176 cm (1.76 m) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818$ kg/m^2.

Results for BMI will be expressed with 1 decimal place and rounding is allowed. The above value should be captured as 25.6 kg/m^2 in the database.

9.1.5 Vital Sign Procedure

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw. Vital signs assessments will be collected with a window of ±15 minutes.

Vital signs consisting of body temperature (oral), respiration rate, blood pressure and pulse will be measured in a seated resting state (≥10 minutes).

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Cerevance. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and as stipulated in the Schedule of Study Procedures (Appendix A). Abnormal Screening labs may be repeated once at the discretion of the investigator for assessment of eligibility. Subjects who still do not meet eligibility criteria may be re-screened at investigator's discretion.

Table 9.a lists the tests that will be obtained for each laboratory specimen. Additional laboratory assessments may be performed at the Investigator's discretion and entered in the database for Randomized Subjects only, if the results are deemed Clinically Significant by Investigator.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets Prothrombin time /INR/Partial thromboplastin time (PTT)	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc

Diagnostic Screening:		
Serum	**Urine**	**Saliva (d)**
Serum hCG (a) At Screening Only: Hepatitis panel, including HBsAg and anti-HCV FSH (b)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c)	Alcohol cotinine

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, RBC=red blood cells, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L to obviate the need for contraception.
(c) To be performed at Screening.
(d) Alcohol and cotinine saliva samples may be collected, if needed.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

All laboratory safety data will be transferred electronically to Cerevance or designee in the format requested by Cerevance. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results into the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the PI or sub-investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

During the study and for 12 weeks after last dose of study medication, nonsterilized males and female subjects of childbearing potential who are sexually active must agree to use two effective methods of contraception.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1-year post-vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

The following are acceptable forms of contraception:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly).
- Diaphragm (plus spermicidal cream or jelly).

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.

Hormonal Contraception (stable regimen)

- Birth control pills or patch.
- Injected hormonal contraceptive (such as Depo-Provera).
- Vaginal hormonal ring (such as NuvaRing).

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive guidance with respect to the avoidance of pregnancy. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication. Male subjects must be advised not to donate sperm from signing of informed consent to 12 weeks after the last dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects who have only received placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded in a supine position resting for at least 10 minutes at Screening to assess eligibility. The ECGs will be recorded in triplicate at approximately 5-minute intervals, with a window of ±2 minutes. The investigator (or a qualified physician at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. A copy of the ECG trace should be kept with the subject's notes.

ECGs will be read automatically and also, the investigator or sub-investigator or a suitably qualified delegate will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal NCS, or abnormal and CS. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary.

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.12 Pharmacogenomic Sample Collection

Every subject must sign informed consent/be consented in order to participate in the study, but consent to participate in the pharmacogenomic sample collection (genetic substudy) is optional.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN058.
- Finding out more information about how CVN058 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN058.
- Identifying variations in genes related to the biological target of CVN058.

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN058 and other study medications, and for improving the efficiency, design and study methods of future research studies.

The DNA samples will be used to evaluate common variations in genes which encode drug metabolizing enzymes and transporters. This could be helpful in understanding why there are differences in CVN058 kinetics between subjects. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Whole blood will be collected and stored for possible DNA or RNA isolation and analysis.

DNA sample collection:

> One 6 mL whole blood sample will be collected before study drug dosing on Day 1 of Period 1 only from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K2EDTA) spray-coated tubes, and stored under frozen conditions.

RNA sample collection:

> Two whole blood samples (2.5 mL per sample) will be collected from each subject into a PAXgene tube on Day 1 of each period at pre-dose and post EEG for RNA pharmacogenomic analysis.

If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 7-digit subject ID. Detailed instructions for the handling, shipping, and storage of pharmacogenomic samples will be provided in the lab manual.

The samples will be stored for no longer than 15 years after completion of the CVN058 study and/or until the drug development of CVN058 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Cerevance.

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) will be collected for analysis of CVN058, and its metabolite if appropriate; plasma will be collected into chilled vacutainers containing

K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment will be provided in the lab manual.

Serial blood samples for determination of CVN058, and its metabolite if appropriate, in plasma will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for CVN058 Pharmacokinetic Analysis

Sample Type	Dosing Day	Time Post-dose (hours)
Plasma	1	Pre-dose (within 15 minutes prior to dosing), 1hour post-dose (pre-EEG), and 5 hours post-dose (post-EEG)

The PK samples will be collected before any other assessments are performed, if scheduled at the same time point. The actual time of sample collection will be recorded on the source document and eCRF.

Placebo samples will not be analyzed by the bioanalytical laboratory except 1 sample per subject receiving placebo around the expected time at which CVN058 C_{max} is expected to occur to ensure from a safety perspective that no subjects have inadvertently received active treatment.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of CVN058 will be measured by high-performance liquid chromatography with tandem mass spectrometry. If appropriate, plasma samples analyzed for CVN058 also may be analyzed for the CVN058 metabolite.

9.1.14 Pharmacokinetic Parameters

The PK parameters of CVN058, and its metabolite (if appropriate), will be derived using non-compartmental analysis methods. The PK parameters will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN058, and its metabolite if appropriate, in plasma. Other parameters may be calculated as appropriate.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from time 0 to 5 hours post dose.
C_{max}	Maximum observed plasma concentration.
t_{max}	Time to reach C_{max}.

9.1.15 Pharmacodynamic Sample Collection

MMN will be used as a PD assessment. At each testing session, the following PD assessments will be performed during the EEG: MMN, P50, gamma power, and P300. Collection of P50 may be omitted if the essential equipment is not available. The testing session during each Treatment Period will begin approximately 1.5 hours after administration of study drug.

9.1.16 Pharmacodynamic Parameters

All EEG parameters will be obtained in accordance with the EEG acquisition guideline provided by Cerevance or their designee. It is anticipated that each EEG procedure will take approximately 4 hours to complete, including approximately 30 minutes to set up, 3 hours acquisition time, and 30 minutes to clean up.

MMN

MMN is a pre-attentive auditory component elicited by deviant stimuli in an auditory oddball task. MMN predominantly reflects activation of neuronal ensembles within primary auditory cortex, and thus indexes sensory level disturbance in schizophrenia. MMN will be obtained independently to pitch and duration deviant stimuli. MMN is maximal at frontocentral electrodes (Fz, Cz). Mean peak amplitude at 5 electrodes surrounding Fz within a predefined latency range will be the primary outcome measure.

P50

P50 auditory evoked potentials will be recorded. Participants will be seated and instructed to relax and to focus their eyes on a fixation point. Stimulus signal of 90-dB pulses of 0.1 msec in duration will be generated and recorded the event-related potential waveforms.
32 pairs of auditory clicks will be presented every 10 seconds, with a 500 msec interclick interval.

[redacted]

Quantitative Electroencephalogram, Gamma Power

Five-minute eyes open/close recordings will be obtained during each recording session. Ten 1-second, artifact-free epochs will be chosen for quantitative analysis. Primary outcome measures will consist of power within delta (0.5 – 4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (13-20 Hz), low gamma (20-40 Hz) and high gamma (40 – 60 Hz) over predesignated frontal, central, temporal and occipital sites. In addition, specific measures of 40 Hz activity will be assessed in response to repetitive 40 Hz auditory stimulation.

P300

As opposed to MMN, which are obtained under passive (i.e., no-task) conditions, auditory P300 will be obtained only when subjects must attend to and detect novel task-relevant deviant stimuli. Generators for P300 are located in distributed frontoparietal networks and so represent an index of higher order, “cognitive” processing in schizophrenia. P300 will be obtained to deviant auditory stimuli in an auditory “oddball” paradigm. P300 is maximal in amplitude at Fz and Pz

electrodes. Primary outcome measures will consist of peak amplitude within prespecified latency range at the frontal/parietal sites.

9.1.17 Positive and Negative Syndrome Scale

The PANSS was developed and standardized for typological and dimensional assessment of schizophrenic phenomena. In this study, empirically derived factors are tested excluding those items that could not be assessed during the test sessions: positive symptom factor (delusions, unusual thoughts, somatic concern, grandiosity, suspiciousness, and hallucinations), negative symptom factor (emotional withdrawal, blunted affect, poor rapport, disturbance of volition, preoccupation, and motor retardation), cognitive factor (difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgment and insight, poor attention, tension, mannerisms, and posturing), hostility (excitement, hostility, impulse control, and uncooperativeness), emotional discomfort (depression, anxiety, and guilt). PANSS will be collected at Screening, Early Termination, and at the Follow-up Visit if clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

The duration of the PANSS is approximately 30 minutes (Kay, 1990).

9.1.18 Columbia Suicide Severity Rating Scale

The determination and management of subjects' suicidality risk is the Investigators' responsibility. For study purposes, suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Mundt, 2013).

The C-SSRS is a 2-page questionnaire that prospectively assesses suicidal thoughts and behavior using a structured interview for patient responses. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt).

Different versions of the scale are available. In this study, "Baseline/Screening" version will be used at Screening Visit and "Since last visit" version at all subsequent visits. "Since the last visit" should collect information from the last visit where C-SSRS was administered. If the patient's response generates a change in the findings report from negative to positive, the patient should be referred for immediate psychiatric evaluation on the same date as the site visit. Positive suicidality findings, if confirmed by the PI, is considered to be a serious event. If arising after signing informed consent but prior to administration of any study medication, it is considered a Pretreatment Event (PTE). If arising after administration of any study medication, it is considered an SAE.

The C-SSRS will be administered by the PI or a trained designee on paper and captured in the eCRF. The same interviewer should be used throughout the study for the same subject where possible.

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail Screening should not be reused.

9.1.20 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. Randomization will take place on Day 1 of Treatment Period 1.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects with schizophrenia including schizoaffective disorder will be screened within 28 days prior to enrollment. All subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screen failures. Following written informed consent, Screening procedures may be conducted on different days. Assessments to be conducted during the Screening period are outlined in Appendix A.

9.3.2 Treatment Phase

The treatment will be administered over 3 Periods, separated by 7-10 days for washout. Assessments to be conducted during the screening period are outlined in Appendix A.

9.3.3 Final Visit/End of Treatment

The Final Visit additional assessments will occur prior to Discharge from the clinic at the end of Treatment Period 3, Day 1, as outlined in Appendix A.

For all subjects who received any study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The procedures outlined in Appendix A will be performed and documented.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by telephone approximately 7-10 days after receiving the last dose of study medication (Treatment Period 3) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. The genetic material will be preserved and retained by a biorepository contracted by Cerevance for up to but not longer than 15 years or as required by applicable law.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study. During the "storage" stage, the sample will be used in the analysis of the study drug and related disease states. At this stage, sample and data are linked to personal health information with code numbers. This link means that subjects may be identifiable but only indirectly. The code numbers will be kept secure by the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening (x1)	Number of Samples per Period (x 3 Periods)	End of Treatment	Total Volume (mL)
Safety Laboratory Samples (a)	12.5	1	--	1	25
Hepatitis Panel	5	1	--		5
FSH (b)	3	1	--		3
PK Samples	6	--	9	--	54
DNA Sample	6	--	1 (c)	--	6
RNA Samples	5	--	6	--	30
Total Blood Sampling Volume (per Study)					123

(a) Includes Hematology, serum chemistry, and coagulation panel.

(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e. last regular menstrual cycle >2 years) and not surgically sterile.

(c) Only collected in Day 1, Period 1.

The maximum volume of blood at any single day is approximately 40 mL, and the approximate total volume of blood for the study is approximately 123 mL.

Direct venipuncture is the preferred method of blood collection. Any other method will need to be approved by the Sponsor.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.
- Suicidal Ideation and Behavior:
- A completed suicide is always a SAE based on its fatal outcome. C-SSRS score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) would likely indicate serious suicidal ideation and can be used to trigger intervention procedures to provide urgent care. Such procedures may include further evaluation and appropriate management; and/or immediate contact with (or need for a referral to) the subject's mental health practitioner; and/or possible referral to the emergency room; and/or admission to an in-subject unit. For the purpose of this protocol active suicidal ideation level 4 and 5 should be considered important medical events and reported as serious irrespective of whether the subject was hospitalized or not.
- Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or intention to act will be collected as non-serious adverse events in accordance with the standard AE reporting requirements (e.g., if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE).
- A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the eCRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as a serious adverse event.
- Acts of self-mutilation or self-injury without suicidal intention (i.e., self-imposed cigarette burns), will be collected as non-serious adverse events, unless they meet other seriousness criteria.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
   - Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Medically Significant AE List (Table 10.a).

Table 10.a Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Serotonin syndrome
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE (e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE).

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.

- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication on Day 1 Period 1 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1 Treatment Period 1. Routine collection of AEs will continue until 21 days following last dose.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the

eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Cerevance SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Cerevance SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report, but becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Cerevance personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principle investigator must review the data change for completeness and accuracy, and must sign, and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared to describe and direct study data analyses. The SAP will provide details regarding the definition of analysis variables and analysis methodology to address all study objectives, and will be finalized prior to data analysis.

A targeted data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Blinded Interim Analysis

The original study SAP describes a blinded interim analysis and sample size re-assessment to occur when blinded MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. An analysis structured identically to the Primary Analysis but blinded to treatment, will be performed. For this interim analysis, the MMN negative values closest to zero (i.e., most impaired) and the negative values farthest from zero (i.e., least impaired) for each subject will be selected and compared. This analysis will utilize the O'Brien-Fleming group-sequential stopping boundary to control alpha. SAS Proc SEQTEST will be employed to perform the conditional power analysis for one interim analysis. Study stoppage for futility may occur if conditional power is very low.

Additionally, prior to study stoppage, an assessment will be performed to calculate the conditional power values associated with protocol-permissible increases in the sample size (i.e., up to N=40), based on the observed blinded data at the time of the interim analysis

13.1.2 Unblinded Interim Analysis

During the study, upon review of the outputs from the blinded interim analysis (which included data only from the first 12 subjects, who had already completed the study), the Sponsor determined that an unblinded analysis of those interim data is necessary to properly inform decisions about study continuation and dose selection. Unblinding of the interim analysis data is thus introduced in Protocol Amendment 4, and the SAP will be modified accordingly and finalized prior to the unblinded interim analysis.

An analysis unblinded to treatment and structured identically to the Primary Analysis will be performed using data only from the first 12 subjects, who have already completed the study. The analysis will consist of a comparison of the post dose PD parameter Mean Amplitude of Duration MMN versus the same parameter at time-matched placebo period timepoints. This analysis will utilize the O'Brien-Fleming group-sequential stopping boundary to control alpha.

SAS Proc SEQTEST will be employed to perform the conditional power analysis. Study stoppage for futility may occur if conditional power is very low.

Additionally, prior to study stoppage, the unblinded interim data will be used to calculate the conditional power values associated with protocol-permissible increases in the sample size (i.e., up to N=40), based on the observed unblinded data at the time of the interim analysis.

13.1.3 Analysis Sets

Safety Set

The Safety Set will consist of all subjects who are randomized and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration of CVN058.

Pharmacodynamic Set

The PD Set will consist of all subjects who receive study drug and have at least 1 post-dose PD measurement.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the PK and PD endpoint analyses, but data for all subjects will be presented in the subject listings.

13.1.4 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by sequence and overall. Summary statistics (number of subjects, mean, median, standard deviation, minimum and maximum) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, ethnicity, race, smoking status, and caffeine consumption).

13.1.5 Pharmacokinetic Analysis

The concentration of CVN058, and its metabolite if appropriate, in plasma will be summarized over each scheduled sampling interval using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

Descriptive statistics will be used to summarize the plasma PK parameters for CVN058, and its metabolite if appropriate. In addition, geometric mean and percent coefficient of variation will be computed for C_{max} and AUC_t.

A more detailed analysis will be presented in the SAP.

13.1.6 Pharmacodynamic Analysis

Observed values for the PD parameters (MMN and exploratory PD parameters) will be summarized by treatment and compared to placebo using summary statistics. Comparison of post-dose PD parameters from a time-matched placebo period timepoint will be analyzed using analysis of covariance (ANCOVA) with factors for sequence, subject nested within sequence, period, and treatment. Two-sided 95% confidence intervals will be constructed for the LS mean of observed differences in PD parameters, comparing CVN058 and placebo at a time-matched post-dose time point.

Effect size will be calculated for comparisons of CVN058 to placebo using Cohen's *d* which expresses the difference between the means of 2 groups as a function of their pooled standard deviation.

Exposure-response relationships for CVN058 will be explored graphically.

13.1.7 Safety Analysis

The Safety Set will be used for all summaries of TEAEs, laboratory tests, and vital signs. An increase in weight by 7% should be indicated as Clinically Significant or Not Clinically Significant and assessed on a case by case basis. All safety data will be summarized by treatment.

AEs will be presented in listings. TEAEs will be classified according to system organ class and preferred term and will be tabulated with a breakdown by treatment and by event severity. Similar TEAE tabulations will be performed on those events assessed by the investigator as related to study drug.

Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized by treatment.

Physical exam findings, suicidality assessments (C-SSRS), and PANSS scores will be presented in data listings.

Baseline values will be the latest observation prior to dosing in the first study period. Thus, for most assessments, the Baseline value will be the Day 1 pre-dose observation; for Clinical Laboratory assessments, the Baseline values will be from the Screening Visit (Day -28).

13.2 Determination of Sample Size

Enrollment of 20 subjects with schizophrenia is estimated to provide approximately 80% power to detect a mean effect size of Cohen's d=0.5 with an error rate of alpha=0.10. Discontinued or withdrawn subjects and subjects for whom MMN is not available for all three study periods may be replaced. The sample size chosen of 20 completed subjects is considered to be sufficient to explore the changes in MMN between CVN058 and placebo as well as safety and tolerability of CVN058 in this population.

Sample size re-estimation may occur when MMN data from all 3 periods are available for 12 subjects, or when 20 subjects have been dosed and are expected to complete the study, whichever is sooner. To ensure adequate study power, sample size may be increased based on this re-estimation procedure. Further details will be included in the SAP.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. PK samples collected outside of the intervals (listed in Table 14.a), ECGs, vital signs, and RNA pharmacogenomic samples collected outside of the listed intervals are minor deviations and do not require the Protocol Deviation Form to be completed but must be documented in the subject's source documents. A Protocol Deviation eCRF should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

Protocol Deviations should be captured in the site source document for PK samples collected outside of the following intervals:

Table 14.a Windows for Pharmacokinetic Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes predose	Pre-dose (-0.25 hour)
±5	Postdose 1 hour
±15	Postdose 5 hours

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific Screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet

(if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Cerevance will, at a minimum register interventional clinical trials it sponsors on ClinicalTrials.gov or other publicly accessible websites before start of study. Cerevance contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available

for public viewing. For some registries, Cerevance will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject Screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Cerevance providing this information to callers must provide Cerevance with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Cerevance may post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

		CVN058 and Placebo Treatment Periods 1, 2, and 3 (a)		End of Treatment		Follow-up
Study Day:	**Visit 1: Screening**	**Day 1 pre-dose**	**Day 1 post-dose**	**Period 3, End Day 1**	**Early Termination (c)**	**Day 7-10 After End of Treatment (b)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Reproductive Status	X					
Social History	X					
Medication history	X					
Physical examination	X	X		X	X	
Vital signs (d)	X	X	X		X	
Weight, height, and BMI (e)	X			X	X	
Concomitant medications (f)	X	X	X		X	X
Medical history (g)	X					
Clinical laboratory tests (h)	X			X	X	
Hepatitis panel	X					
Audiometric Screening and Tone Matching test (i)	X					
FSH (j)	X					
Pregnancy test (hCG), serum except as noted	X	X (urine)			X	
Urine drug and saliva alcohol screen	X					
ECG (k)	X					
EEG battery (l)			X			
MMN (m)			X			
DNA sample collection (n)		X				
RNA sample collection (o)		X	X			
PK blood collection (p)		X	X		X	
Study drug dosing (q)			X			
PTE assessment (r)	X	X				
AE assessment (s)			X		X	X
C-SSRS (t)	X		X		X	
PANSS (u)	X		X		X	

Footnotes are on last table page.

(a) Minimum 7-day and maximum 10-day washout period is required in between Treatment Periods 1, 2 and 3.
(b) The Follow-up Visit will occur by telephone 7-10 days after End of Treatment unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Conduct procedures for subjects discontinued early per Protocol Section 7.6. The PK sample should be collected at the Early Termination Visit, if within 1 hour of a scheduled PK time point.
(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, and in Periods 1, 2, and 3 (pre dose [within 30 minutes prior to dosing], and at 1 and 5 hours post dose), and at Early Termination (if applicable), and if clinically indicated according to Investigator discretion at the Follow-up visit. Vital signs will be collected with a window of ±15 minutes.
(e) Height and BMI will be collected at Screening only.
(f) Record all patient medications from Screening and throughout the study.
(g) All new medical history arising after signing ICF should be recorded as PTE or AE.
(h) Clinical laboratory tests (hematology, serum chemistry, urinalysis, and coagulation) will be collected at Screening and prior to check-out at End of Treatment or Early Termination, and at the Investigator discretion if a Follow-up Visit is indicated.
(i) Audiometric Screening assessment conducted according to local practice.
(j) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(k) ECGs will be collected with a window of ±2 minutes.
(l) For the EEG battery, testing will be done at Day 1 starting approximately 1.5 hours post dose for each period and will last approximately 3 hours. NOTE: Subjects should refrain from drinking coffee and smoking approximately 1 hour prior to the EEG assessment until discharge from clinic at the end of the afternoon.
(m) MMN will be the first EEG assessment conducted in the battery. EEG (MMN) assessment will be collected with a window of ±60 minutes.
(n) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to study drug administration on Day 1 of Period 1 only. If isolation of DNA from the first sample was not successful or possible, a second aliquot of blood may be taken, if feasible.
(o) Two 2.5 mL whole blood samples will be collected for each Period (Periods 1, 2, and 3) on Day 1 at pre-dose, and 5 hours post- dose.
(p) Blood samples (6 mL) for PK analyses will be collected at pre -dose (within 15 minutes prior to dosing), and 1 and 5 hours post dose. PK collection for pre-dose will be (within 15 minutes prior to dosing), ±15 minutes at the 1 hour post-dose time point, and ±30 minutes at the 5 hour post-dose time point.
(q) Dosing will only occur on Day 1 of each period, and signals the start of the post-dose Day 1 visit assessments.
(r) PTEs will be collected from signing of informed consent up until dosing on Day 1; PTEs will be captured on the AE CRF page.
(s) Any adverse event with onset or exacerbation after dosing on Day 1 of Period 1 will be captured as an AE or SAE.
(t) The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered after EEG/ERP collection on each dosing day, and End of Treatment or Early Termination (if applicable).
(u) The Screening/Baseline PANSS will be collected at Screening, approximately 5 hours after each dose (post EEG) and at Early Termination (if applicable). PANSS will be collected with a window of ±45 minutes.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form 1572) which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form 1572.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non- standard panel) Screening assessments are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CRF Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.