STUDY PROTOCOL

STUDY TITLE: A Translational and Neurocomputational Evaluation of a D1R Partial Agonist for Schizophrenia

Collaborating Sites: Columbia University/Research Foundation for Mental Hygiene (RFMH), State University of New York (SUNY) Stony Brook, University of Pennsylvania, Yale University

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IND HOLDER: John Krystal, M.D.

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1. ACKNOWLEDGMENT OF THE INVESTIGATORS

PROTOCOL TITLE: A Translational and Neurocomputational Evaluation of a D1R Partial Agonist for Schizophrenia

Version Date: _____

Acknowledgement of the Investigator:

1.) I have read this protocol and agree that the study is ethical

2.) I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines

3.) I agree to maintain the confidentiality of all information received or developed in connection with this protocol

Signature of Investigator: Date:

Name of Investigator (Printed or Typed)

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3. ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependent
CBC	Complete Blood Count
CDSS	Calgary Depression Scale for Schizophrenia
CIFTI	Connectivity Informatics Technology Initiative
CMP	Complete Metabolic Profile
CNS	Central Nervous System
C-SSRS	Columbia-Suicide Severity Rating Scale
D1R	Dopamine Receptor 1
D1R/D5R	Dopamine Receptor 1/Dopamine Receptor 5 Family
DICOM	Digital Imaging and Communications in Medicine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
FC	Functional Connectivity
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
FTND	Fagerstrom Test for Nicotine Dependence
GABA-A	gamma aminobutyric acid-A
GBC	Global Brain Connectivity
GCP	Good Clinical Practice
GUID	Globally Unique Identifier
hcG	Human Chorionic Gonadotropin
HIC	Human Investigations Committee
HIV	Human Immunodeficiency Virus
HCP	Human Connectome Project
HRF	Hemodynamic Response Function
ICH	International Conference on Harmonization
IRB	Investigational Review Board
IRF	Impulse Response Function
IUD	Intrauterine Device
Ki	Inhibitory constant
MRI	Magnetic Resonance Imaging
NDA	NIMH Data Archive
NIFTI	Neuroimaging Informatics Technology Initiative
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PANSS	Positive and Negative Syndrome Scale
PennCNB	Penn Computerized Neurocognitive Battery
PFC	Prefrontal Cortex

PI	Principal Investigator
PRA	Penn Reading Assessment
QTc	Corrected QT interval on an electrocardiogram
rsfMRI	Resting State Functional Magnetic Resonance Imaging
SAE	Serious Adverse Event
SCID-V	Structured Clinical Interview for DSM-5
sWM	Spatial Working Memory
SCZ	Schizophrenia
XNAT	Extensible Neuroimaging Archive Toolkit
YCCI	Yale Center for Clinical Investigation

4. TRIAL SUMMARY

Title	A Translational and Neurocomputational Evaluation of a D1R Partial Agonist for Schizophrenia
Protocol Short Title	TRANSCENDS
Funding Sponsor	National Institutes of Health (NIH)/ National Institute of Mental Health (NIMH)
IND Holder	John H. Krystal, M.D.
Principal Investigators, Site Program Directors	**Principal Investigators:** John H. Krystal, M.D., Alan Anticevic, Ph.D. **Site Program Directors:** **Columbia University/Research Foundation for Mental Hygiene (RFMH):** Joshua T. Kantrowitz M.D. **State University of New York (SUNY) Stony Brook:** Anissa Abi-Dargham, M.D. **University of Pennsylvania:** Raquel Gur, M.D., Ph.D. **Yale University:** John H. Krystal, M.D., Alan Anticevic, Ph.D.
Medical condition under investigation	Early Episode Schizophrenia
Purpose of study	To test if CVL-562, a D1 partial agonist novel compound, affects working memory neural circuits in patients with early episode schizophrenia.
Study Intervention	CVL-562 in doses of 1 mg, 4 mg, 15 mg and 25 mg, or placebo
Primary objective	To assess the response of cognitive neural circuits to CVL-562 in early episode schizophrenia
Secondary objectives	To assess changes in spatial working memory performance, additional responses of cognitive neural circuits, and to assess factors contributing to individual responses to CVL-562.
Endpoints	**Primary Endpoint:** Spatial working memory neural circuit blood oxygen level dependent (BOLD) signal change. **Secondary Endpoints:** 1. Identification of a proportion of participants with a BOLD signal response to CVL-562 2. Spatial working memory performance change 3. Change in BOLD signal regression with trial-by-trial spatial working memory performance 4. Functional connectivity during spatial working memory performance change 5. Global brain connectivity change 6. Global brain connectivity change comparison with

	genomic maps relevant to psychotic disease processes **Exploratory Endpoint:** Association of genetics with treatment response
Sample size	100 (120 who are eligible for full study procedures will be recruited)
Summary of eligibility criteria	**Inclusion:** - Between the ages of 18 (including 18 years of age) and 45 (up to 45 years and 11 months) at the time of baseline study visit. - Able to provide informed consent (as established by consent interview), and voluntary, signed informed consent prior to the performance of any study-specific procedures - Willing and able to perform study-relevant clinical assessments and Magnetic Resonance Imaging (MRI) as assessed by research staff. - Meet Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder on the basis of the Structured Clinical Interview for DSM-5 (SCID-5). - Be within 10 years of the onset of psychosis based on clinical assessment at the time of Visit 1. - Treatment seeking and willing to accept the constraints on treatment entailed by the study. - Able to demonstrate a basic ability to follow spatial working memory task instructions and perform necessary related motor functions. - Demonstrate a premorbid IQ of ≥80 based on the Penn Reading Assessment (PRA) (1). The PRA correlates with other measures of IQ including the Wide Range Achievement Test (WRAT), but is computerized, based in the laboratory of co-investigators Ruben C. Gur and Raquel E. Gur, and brief to administer, allowing us to lessen the assessment burden on an already lengthy first visit. - Be fluent in English as assessed by research staff. - Clinically stable treatment for at least two months prior to Visit 1 (no hospitalizations, or current suicidal/homicidal active ideation, intent, or plan). - On a stable psychotropic medication regimen (can include no psychotropic medications) for at least 3 weeks prior to Visit 1, and willing to maintain an unchanged regimen during the study. If on depot antipsychotics, participants must have stable dosing for at least two consecutive injections (including the most recent one) as the most recent injections. If on Invega Trinza, there must be no plans to change dosing during the course of the study. - For women of child bearing potential, no intention to become pregnant during the study period, and agreement to use a reliable method of birth control (e.g. Intra-Uterine Device (IUD), hormonal contraception, abstinence, condoms) during the study

	period. Women will be asked to continue their method of contraception for 1 month after receiving their final dose of medication. Any individual who becomes pregnant during the study will be immediately removed, and discussion of the risks and benefits of ongoing pharmacotherapy will proceed on purely clinical grounds.
	Exclusion: - Any unstable medical, psychiatric, or neurological condition (including active or otherwise remarkable suicidal or homicidal ideation) that may necessitate urgent treatment. Active medical conditions that are minor or well controlled are not exclusionary if they do not affect risk to the patient, metabolism of study drug, or the study results (e.g. well-controlled type II diabetes or hypertension) as per the judgment of the investigator. - Be currently treated with any of the following: olanzapine, clozapine, ziprasidone or asenapine, in order to avoid prominent D1 receptor effects. - Any major neurological disease, brain injury, epilepsy, or history of severe head trauma, including concussion with loss of consciousness greater than or equal to 15 minutes, or of psychosurgery. - History of significant cardiac disease (ex: ischemia, arrhythmia). - Any clinically significant abnormality on baseline medical screening tests (electrocardiogram (EKG), complete blood count with differential (CBC), complete metabolic profile (CMP). - Hepatitis B or C (by report or testing) in the presence of abnormal liver function tests - Human Immunodeficiency Virus (HIV) or Acquired Immune Deficiency Syndrome (AIDS) (by report or by testing) due to cognitive effects of HIV and AIDS. - Baseline EKG showing prolonged QTc interval (>450 for males, >470 for females, Framingham correction(2)), with repeat measurement showing the same abnormality. - Current mood episode meeting criteria for a major depressive episode or a manic or hypomanic episode. - History of electroconvulsive therapy (ECT) or treatment with neurostimulation in the past 6 months, or with plans to begin either such treatment during the study. - History of ADHD pre-morbid to the onset of psychosis or other psychiatric illnesses that may be accompanied by cognitive impairments. - Meeting SCID-5 moderate or severe substance use disorder for any substance other than nicotine within the 3 months prior to the initial assessment. - Positive urine toxicology testing for any substance other than marijuana or those prescribed for medical reasons at Visits 1-6. - Pregnancy or intention to become pregnant during the study. - Lactating/breast-feeding or intending to do so during the study - Any non-MRI compatible metal in the body or other

	contraindication to MR imaging. A copper IUD is allowable if permitted by local MRI practices. - Severe claustrophobia, back pain, morbid obesity, or other condition that may make an extended MR session difficult or lead to excessive movement during the imaging session. - Color blindness, strabismus or other uncorrectable visual problems. Those wearing glasses would be asked to use MRI-safe glasses. - Daily use of the following medication within 10 days prior to the initial visit or during the study: Long-acting nighttime or daytime gamma aminobutyric acid-A (GABA-A) receptor facilitators; anticonvulsant medications used at high doses or for seizure control, or psychostimulants or medical cannabis. Participants can be re-assessed for eligibility once they have been free of daily use of these medications for >10 days. Participants may take non-GABAergic sleep medications, short-acting GABA receptor facilitators (benzodiazepine, non-benzodiazepine) prior to and during the study. - Any change in type or dose of psychotropic medications within 3 weeks prior to initial visit or during study to avoid transient effects of medication regimen change. Medication type and dose will be carefully recorded and used as a covariate in analyses. Participants can be re-assessed for eligibility once they have been on a stable dose of medication for >3 weeks. - CVL-562 is metabolized by P450 CYP3A4. In order to avoid pharmacokinetic interactions, medications or substances that induce (barbiturate, carbamazepine, etc.) or are moderate-strong inhibitors (ketoconazole, etc.; grapefruit juice) are excluded if used within 10 days prior to or during study. Participants can be re-assessed for eligibility once they have been free of these medications/substances for >10 days. - Active attempts to discontinue smoking, vaping or other nicotine products within the 3 weeks prior to study or during the study. Participants can be re-assessed once quit attempt is stable. - Diastolic blood pressure >95 or <50 mmHg or systolic blood pressure > 170 or <80 mmHg with repeat measurement showing the same abnormality. - History of allergy or other contraindication to the proposed pharmacotherapy. - Other medication treatment with which proposed pharmacotherapy is contraindicated, in the opinion of study psychiatrists or of a subject's prescribing psychiatrist.
Assessments	- Structured clinical interview (SCID-V) - Spatial working memory task - The Positive and Negative Syndrome Scale (PANSS) - Penn Computerized Neurocognitive Battery (PennCNB) - Urine toxicology - Urine pregnancy - Baseline bloodwork (complete blood count with differential,

	comprehensive metabolic panel, Hepatitis B, Hepatitis C) - Electrocardiogram (EKG) - Vital signs - Physical exam - Penn Reading Assessment (PRA) - Fagerstrom Test for Nicotine Dependence (FTND) - Calgary Depression Rating Scale - Beck Anxiety Inventory - Columbia-Suicide Severity Rating Scale (C-SSRS; baseline/screening and since last visit versions) - Edinburgh Handedness Inventory - Lifestyle Questionnaire - Drug assay bloodwork - fMRI scans

1. TRIAL DESIGN / STUDY SCHEMA

Patients (n=120 who are eligible for full study procedures) will be recruited from four centers experienced in recruiting and enrolling patients with early episode psychosis into research (Columbia University/Research Foundation for Mental Hygiene (RFMH), SUNY Stony Brook, University of Pennsylvania, Yale University). Patients will be recruited over a two-three year period. Study participation for patients will last approximately one-two months.

Upon successfully completing the initial phone screening process, participants will be invited to complete a baseline assessment to determine eligibility. Including this baseline assessment, all eligible participants would complete 7 total study visits (of which some may occur over multiple days). Five of these will be test visits involving the administration of CVL-562 (immediate release formulation) or placebo. Each test visit start time will be separated by at least 48 hours (six half-lives of CVL-562). The baseline visit will involve informed consent and screening assessments to determine eligibility, including a structured clinical interview (SCID-V), Penn Reading Assessment (PRA), Edinburgh Handedness Inventory, PANSS, PennCNB letter n-back task, Calgary Depression Scale for Schizophrenia, Beck Anxiety Inventory, Columbia-Suicide Severity Rating Scale—baseline/screening version (C-SSRS, baseline/screening), urine toxicology/pregnancy, baseline bloodwork (complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), Hepatitis B & C, HIV, genetics (optional)), EKG, vital signs, health history, physical exam, practice spatial working memory task, practice flashing checkerboard task, MRI safety assessment and an optional mock scanner experience. Subjects will be randomized to the order of doses of CVL-562 (1 mg, 4 mg, 15 mg, or 25 mg) or placebo for the next 5 visits. The randomization would occur after eligibility for full study procedures is confirmed, and would assign 75% of patients to the highest dose on the last visit. 25% of patients would receive the highest dose on one of the other four visits. This randomization strategy is intended to minimize the impact of association of the 25 mg dose with nausea in approximately 30% of subjects, which may unblind subjects and lead to study discontinuation. All female participants will be required to be on birth control (or abstinence) and will receive pregnancy tests at the start of each visit. Information on nicotine use, the amount and duration of use will be collected at the start of the study using the Fagerstrom Test for Nicotine Dependence Questionnaire. All subjects will be tested for COVID-19 as part of Visit 1. COVID-19 testing may be repeated after Visit 1 based on symptoms.

Each test visit will begin with clinical assessment to confirm continued eligibility for the study, including urine sample for toxicology/pregnancy exam, Positive and Negative Syndrome Scale (PANSS), Columbia-Suicide Severity Rating Scale—since last visit (C-SSRS, since last visit), MRI safety assessment, and vital signs. If participants have not eaten a meal within two hours prior to the start of the study visit, they will be given a small meal to induce a fed state, as the effects of the study drug have a different timeline during a fed vs. fasting state. A lifestyle

questionnaire will be administered to understand basic events that occurred in the hours before the scan. A brief refresher session on the spatial working memory task will be presented to the participants to remind them of the task instructions at this point or after drug administration prior to the start of scanning. After these procedures, the test visit medication will be administered and the subject will enter the fMRI scanner to perform the spatial working memory task. Vital signs will be taken after drug administration and prior to scanning. Scanning is timed to have functional imaging coincide with peak CVL-562 plasma levels, i.e., it will begin approximately 75 minutes following medication administration and last for approximately 90 minutes (up to 2 hours). Plasma levels of CVL-562 will be obtained prior to and following imaging with a blood draw or IV continued during the scan to minimize frequency of needlesticks. Vital signs, PANSS, C-SSRS—since last visit, and PennCNB will be administered immediately following removal from the scanner. All subjects will be observed for at least 2 hours following dosing, and provided follow-up (see below, Protection Against CVL-562 Risks).

After completion of the 5 treatment visits, participants will be scheduled for a final in-person follow-up visit to conduct an exit interview with debriefing of the study.

2. RATIONALE AND BACKGROUND

2.1 Disease

Schizophrenia (SCZ) is a disabling neuropsychiatric illness characterized by disturbances in perception of reality and substantial cognitive impairment (3). The illness affects approximately 1% of the population, and is highly debilitating given the effects of the illness on cognition, sensory perception and social/motivational functioning. Cognitive disturbances are considered to be one of the main reasons for enormous functional disability in patients with schizophrenia and associated psychotic illnesses. The overarching aim of this protocol is to further investigate areas of cognition impaired in schizophrenia, particularly spatial working memory as assessed with functional neuroimaging (4, 5). This study proposes to examine the effects of CVL-562, a dopamine-1 receptor partial agonist, on the neural signal of brain regions involved in cognition in patients with schizophrenia, and related psychotic disorders. The primary objective of this study is to understand the neural circuit targets of this compound as it relates to improving cognition in schizophrenia and related psychotic disorders. A secondary outcome will be to measure the effect on spatial working memory performance, and secondary outcomes will examine effects on functional connectivity. All patients will be between 18-45 years old, and psychiatrically stable with early course (psychotic symptom onset within the past 5 years) schizophrenia spectrum disorder (e.g. schizophrenia, schizoaffective disorder, or schizophreniform disorder and will have working memory deficits (defined as below average performance on the letter n-back task of the PennCNB battery). As part of the study, they will receive oral administration of specified doses in a random order with repeated functional magnetic resonance imaging and cognitive testing during those visits. The most common side effects of

this compound are nausea and headache. This is a multi-site study that requires the efforts of 4 study sites in total (Columbia, SUNY Stony Brook, UPenn, and Yale), and we aim to have a total recruitment effort of 120 subjects who are eligible for full study procedures.

2.2 Pharmaceutical and Therapeutic Background

2.2.1 D1 and D5 receptor function are critical for optimal cortical function.

All D1R agonists studied to date activate both D1 and D5 receptors. D1R/D5R agonism is one of the most intensively studied therapeutic mechanisms from a basic neuroscience perspective, but least understood mechanisms from a clinical perspective. Patricia Goldman-Rakic first identified procognitive effects of D1R/D5R agonism in non-human primates (6). Yet, we have not succeeded in developing D1R/D5R treatments for schizophrenia for reasons that may include: i) only very recent development of D1R/D5R agonists with good CNS bioavailability, ii) steep inverted-U dose-related effects of D1R/D5R agonists on working memory (WM) make optimal dose selection difficult (7), ii) the acute behavioral effects of D1R agonists may not be indicative of their effects in D1R-sensitized networks (8), iv) chronic antipsychotic treatment may downregulate D1Rs and complicate the optimal dosing of D1R agonists in patients (7), v) preclinical and computational studies make specific predictions about D1R/D5R agonist effects (9-11) but clinical studies have tested these drugs using standard neuropsychological tests that were not optimized to detect D1R agonist effects (12), and vi) illness phase may influence D1R/D5R agonist response (13). For instance, there is evidence that early course patients may exhibit more severe cortical functional hyperconnectivity (14, 15) but less of the progressive cortical volume loss, and presumably synaptic loss, associated with chronic illness (16-18). Below, we address strategies arising from translational neuroscience, computational neuroscience, and precision medicine that may help to address limitations of prior efforts to develop D1R/D5R agonist treatments for cognitive impairment in schizophrenia.

2.2.2 The role of D1 receptors in cognitive impairment in schizophrenia.

The translational framework underlying this application is that D1R/D5R agonists improve cognition and, more specifically, working memory (WM) in schizophrenia by restoring deficient inhibitory tuning of prefrontal cortical (PFC) networks. Both early course schizophrenia and healthy subjects administered ketamine exhibit increased resting PFC functional connectivity (FC) (14, 19) and reduced precision of information encoded in WM (20, 21). PFC inhibitory tuning deficits in schizophrenia might arise, in part, from deficits in excitatory drive to interneurons (22). However, these tuning deficits may be exacerbated by deficient PFC D1R/D5R signaling. A Consortium co-investigator, Dr. Abi-Dargham and colleagues showed that schizophrenia patients have deficits in prefrontal cortex (PFC) dopamine release and upregulation of D1R/D5Rs in association with WM deficits, implicating deficits in D1R/D5R signaling in cognitive dysfunction in

schizophrenia (23-25). Goldman-Rakic, Arnsten, and colleagues showed in non-human primates that deficits in D1R/D5R signaling reduce neural tuning during WM (26). In turn, they demonstrated that D1R/D5R agonists restore the sculpting of neural activity associated with spatial WM (sWM) and suppress FC of neighboring pyramidal neurons (i.e. unwanted hyperconnectivity) (27, 28). Using a delayed response sWM task, they also showed that D1R/D5R agonists attenuated sWM disruption produced by chronic haloperidol administration (29)(, amphetamine sensitization (11), ketamine administration (30), and aging (31). Computational models of this circuit show that, while enhancing tuning, D1R/D5R agonism stabilizes recurrent neural activity and reduces effects of distractors (32). The aims below test translational hypotheses designed to validate biomarkers for future human D1R agonist trial development.

Therefore, we hypothesize that the D1R/D5R partial agonist CVL-562 will have pro-cognitive effects in schizophrenia by restoring inhibitory tuning of prefrontal cortical activity, thereby increasing sWM behavioral precision and reducing the impact of distractors. Prior studies from investigators within this Consortium (AA, JL, RG, JVS) using the full D1R/D5R agonist, DAR-100A described promising behavioral effects in schizophrenia and schizotypy, but they were unable to validate a neural functional biomarker of target engagement (12, 33). Moreover, clinical effects in these initial studies were insufficiently robust to drive further development. CVL-562 presents many advantages for psychopharmacology research relative to DAR-100A. Thus, we are at a key junction where we need to identify biomarkers sensitive to changes in D1R/D5R function that can definitively guide drug development, leading to clear Go/No-Go decisions with respect to subsequent, full-scale clinical trials.

2.2.3 CVL-562 is a long-awaited selective D1R/D5R partial agonist.

Prior D1R/D5R agonists studied in schizophrenia included SKF38393, a weak partial agonist with poor CNS bioavailability (34) that produced ambiguous results (35), and dihydrexidine/DAR-100A, a full agonist at both receptors (35) with very steep inverted U dose-related effects and unclear benefits (12). D1R full agonists are limited by tachyphylaxis and tolerance. CVL-562 is a partial agonist that is relatively resistant to engaging the b-arrestin pathway and has substantially reduced liability to produce tachyphylaxis and tolerance (36). CVL-562 has high selectivity for D1R/D5R and moderate binding affinity for both recombinant hD1R (Ki = 95 nM) and hD5R (Ki = 175 nM) (37) (unpublished Pfizer data). In vitro functional testing against recombinant hD1 and hD5 receptors established that the compound is an agonist, which stimulates cAMP formation with EC50 values of 580 nM and 220 nM, respectively. Comparison of the cAMP response to the full agonist, dopamine, indicated that CVL-562 is a partial agonist at D1Rs and D5Rs with intrinsic activity values of 44% and 74% for the hD1 and hD5 receptors, respectively. With oral administration, it has a Tmax of 60-90 min, half-life of 7.5 h, and it is provided in 1, 3 and 5 mg tablets. Its tolerability and efficacy was demonstrated preliminarily in a positive study in Parkinson disease where a single

administration produced 12 hours of clinical improvement (35). It was developed by Pfizer, Inc. and recently acquired by Cerevel Therapeutics, who have agreed to support the proposed trial. As noted above, CVL-562, like all prior pro-cognitive D1R agonists, also stimulates D5R. D5Rs are located on proximal dendrites, while D1Rs are located on dendritic spines and distal dendrites (38). D5R, like D1R, plays an important role in sWM (39). We are taking several steps in this study to address potential implications of the dual actions of CVL-562. First, we are densely mapping the dose-response curve for CVL-562 from marginal occupancy to the limits of tolerability to determine whether there are non-linear (inverted-U) dose-related effects. The moderate intrinsic activity of CVL-562 at D1R may protect against detrimental effects of cognition related to overstimulation of D1R and direct impairment of cognition was not observed in the Pfizer Phase IB SCZ trial. However, it is still possible that this drug produces detrimental effects on cognition (inverted-U dose-response) at given doses due to overstimulation of D5R. Therefore, our study design incorporates a wide range of doses to identify individual responses to each dose and allow us to map individual pharmacologic dose-response profiles.

2.2.4 Ability of responses to single doses to predict the effects of chronic dosing.

Unfortunately, the initial Phase IB study of CVL-562 in schizophrenia produced negative results and did not provide guidance for dose-selection. Differences between this earlier study and the current study are that we believe that we would optimize patient selection, use more sensitive outcome measures, and map the dose-response relationship more precisely. Prior non-human primate studies, though, describe dose-related improvements in sWM (40), and with chronic intermittent administration, even lower doses of D1R/D5R agonists that were without initial benefit also came to have procognitive effects (32). Thus, we are confident that doses of CVL-562 that produce acute neural signatures of improvement, and secondarily, improvement in sWM would be likely to produce clinical benefits in a subsequent longer clinical trial. As our primary endpoints are imaging in nature, we are also testing to see whether D1 partial agonism affects sWM circuits, with improved sWM performance and the identification of a subset of those who respond to CVL-562 as secondary endpoints. Using these as secondary endpoints could be used in subsequent full-scale clinical trials if our study demonstrates single-dose effects of CVL-562 on associated neural circuits.

2.2.5 Adjusting for antipsychotic effects.

Antipsychotics could complicate this study in three ways: directly competing with dopamine for D1Rs, down-regulating D1Rs and D5Rs (7) and reducing cortical structural connectivity, which might be reflected in antipsychotic-related reductions in cortical volumes (41, 42). To reduce the first risk, we are excluding antipsychotics with high D1R affinity, including olanzapine, clozapine, ziprasidone and asenapine. The second risk is somewhat unavoidable, as D1R/D5R down

regulation occurs as early as 6 months of antipsychotic treatment (7). Nonetheless, it is essential to determine the benefits of adjunctive CVL-562 in patients engaged in antipsychotic treatment so that findings can generalize to typical treatment settings. However, to minimize the second and third risks, we will limit this study to people early in the course of schizophrenia to limit the cumulative impact of antipsychotic exposure. One additional potential risk is of pharmacokinetic interactions of CVL-562 and antipsychotic medications. CVL-562 is primarily metabolized by the P450 enzyme CYP3A4 (Investigator Brochure). We do not anticipate drug-drug interactions with antipsychotics because neither CVL-562 or the antipsychotics allowed for patients in this project are P450 enzyme inhibitors or inducers (Investigator Brochure). Nonetheless, we will measure plasma CVL-562 levels on each test visit and we will explore whether plasma level is a better predictor than dose of drug effects on our primary and secondary outcome measures. If plasma level is significantly better than dose in predicting biomarker changes, the subsequent clinical trial could target plasma level rather than dose, a strategy that seems to be optimal for some other medications (43).

2.2.6 Optimizing task selection.

This application builds on specific ideas of how D1R/D5R agonists enhance spatial working memory (sWM): 1) they stabilize persisting neural representations over temporal delays and in the face of distraction, 2) they optimize the inhibitory tuning of neural representations, sculpting more precise sWM representations. To optimize both features, we propose a task that is a direct translation of the spatial delayed response task developed by Funahashi and Goldman-Rakic and employed in subsequent studies of D1R/D5R agonists in the Rakic laboratory and others (44). The human version of the task involves having people move their eyes or direct a joystick to the precise spot where a target stimulus was presented in the presence of distractors of varying proximity to the target. Schizophrenia patients show relatively greater impairment in precision with increasing delay and closer proximity of distractors to targets (21). Using the proposed sWM framework builds on the rich evidence base in non-human primates implicating specific back-translational neurophysiologic mechanisms supporting sWM (45, 46), which can be leveraged for understanding clinical deficits via computational modeling (47-49).

2.3 Rationale for Selected Patients

2.3.1 Precision medicine strategies for optimizing the study population.

This proposal employs two precision medicine strategies: selecting patients with demonstrated WM impairment and limiting recruitment to patients early in their course of illness. Enriching for PFC signaling deficits: D1R/D5R agonists are targeted for SCZ because in these patients, deficits in dopamine release and compensatory upregulation of D1R/D5Rs are associated with WM impairments (23-25). Thus, to formally test whether baseline WM impairments are associated

with differential responses to the study drug, all subjects will be measured on the PennCNB letter n-back task at Visit 1. Individual performance on this task can be compared with drug response during analysis. Illness Phase Specificity: As noted earlier, D1R/D5R agonists enhance inhibitory tuning of PFC pyramidal neurons (32), reducing aberrant cortical functional connectivity, i.e., suppressing "noise." We have previously hypothesized that drugs that have this effect may be relatively more efficacious early in the course of schizophrenia (22), when deficits in inhibitory tuning of PFC pyramidal neurons may be at its most prominent. Further, we had suggested that drugs that attenuate functional connectivity would lose their efficacy in chronic illness because these drugs would exacerbate the damaging impact on network function of illness progression-related loss of gray/white matter and synaptic connectivity (16, 50-53). This hypothesis is supported by early course schizophrenia studies that reported resting-state fMRI (rs-fMRI) functional hyper-connectivity relative to later illness stages (14, 15). Importantly, focusing on the early course illness period reduces the impact of progressive synaptic loss due to advancing illness and the possible cumulative and complex impact of antipsychotic treatment. The notion that drugs that enhance inhibitory tuning might work preferentially early in the course of SCZ is supported by findings with an mGluR2 agonist, which ameliorates symptoms at moderate doses in early course patients (≤3 yr), but which worsens symptoms at high doses in chronic (>10 yr) schizophrenia patients (54).

2.4 Rationale for Dose Selection/Regimen

The trial is set up to have 5 treatment visits, each with single dosing followed by an fMRI scan timed to be at peak blood levels of CVL-562. Subjects will be randomized to the order of doses of CVL-562 (1 mg, 4 mg, 15 mg, or 25 mg, all immediate release formulation) or placebo for the next 5 visits. The randomization will assign 75% of patients to the highest dose on the last visit and 25% would receive the highest dose on one of the other four visits. Only the highest dose (25 mg) will be subject to this pseudo-randomization strategy; all other doses will be randomly distributed. This randomization strategy is intended to minimize the impact on study completion of the association of the 25 mg dose with nausea in approximately 30% of subjects, which may unblind subjects and lead to study discontinuation. The particular doses have been chosen based on prior work using this drug, and in order for the group to have a range of doses to chart a purported 'inverted-U' curve of drug dosing with respect to impact on cognitive functioning. The 1 mg dose has been included in order to catch those participants who are the most sensitive to D1 partial agonism. As we intend to chart the full dose-response for each participant, the selected doses will allow us to catch those participants who are either more or less sensitive to D1 partial agonism, as well as chart differential pharmacodynamics curves. The randomization of dose order will also allow for separation of practice effects, and we can test to ensure that drug effects are stronger than practice effects. As the timing of CVL-562's effects is >30% delayed during a fed state than during a fasting state (per investigator's brochure) we will offer a small meal to those who have not eaten a meal within two hours

prior to the visit start. This is an attempt to achieve a fed state across all participants, and achieve standard pharmacokinetics during the scan.

3. STATEMENT OF PURPOSE/OBJECTIVES

This U01 study is a response to the NIMH Program Announcement for National Cooperative Drug Development Groups (NCDDG) intended to accelerate the development of a high priority therapeutic agent by establishing its dose-related pharmacodynamic effects on biomarkers designed to inform subsequent clinical development. The overall aim is to establish neuroimaging biomarkers of D1R/D5R target engagement to accelerate development of D1R/D5R agonists in humans to treat cognitive impairments that underlie functional disability in schizophrenia, a key unaddressed clinical and public health concern.

3.1 Primary Endpoint

To test if CVL-562 has dose-related effects in schizophrenia patients on putative neural biomarkers of D1R/D5R stimulation. We will examine the dose-specific effects of CVL-562 on blood oxygen level dependent (BOLD) signal change during working memory procedures. The primary outcome measure is an analysis of variance of the dose-dependent effects of CVL-562 on the blood oxygen level dependent signal (BOLD) during spatial working memory. Post-hoc univariate tests will quantify directional dose-related CVL-562 effects.

3.2 Secondary Endpoint 1

To test in how many participants CVL-562 produces a dose-related modulation of BOLD signal during working memory procedures.

3.3 Secondary Endpoint 2

To test if CVL-562 produces a dose-related modulation of sWM behavioral performance collected during fMRI. This will be examined using the behavioral data generated during neuroimaging to quantify dose-related CVL-562 effects on sWM performance both with and without distractors.

3.4 Secondary Endpoint 3

We plan to directly examine the association between trial-by-trial sWM performance and task-evoked BOLD signal by regressing trial-by-trial sWM performance with and without distractors with the relevant BOLD signal.

3.5 Secondary Endpoint 4

We will examine the dose-dependent effects of CVL-562 on the functional connectivity of brain regions during spatial working memory.

3.6 Secondary Endpoint 5

We will examine the dose-dependent effects of CVL-562 on the resting state functional connectivity using a data-driven global brain connectivity (GBC) metric.

3.7 Secondary Endpoint 6

We will compare the change in resting state GBC as a function of CVL-562 dose with the transcriptomic maps from the Allen Human Brain Atlas relevant to risk genes in schizophrenia.

3.8 Exploratory Endpoint

We will conduct exploratory analyses to test whether genetic variants of genes related to dopamine or CVL-562 metabolism relate to changes in BOLD signal in response to CVL-562.

4. STUDY PLAN AND PROCEDURES

4.1 Study Design Overview

Patients (n=120) will be recruited from four centers experienced in recruiting and enrolling patients with early episode psychosis into research (Columbia University/RFMH, SUNY Stony Brook, University of Pennsylvania, Yale University). Patients will be recruited over a total of 2-3 years. Study participation for patients will last approximately one-two months. After an initial phone screen to determine interest and general eligibility, participants will be scheduled for an in-person assessment to confirm full eligibility. Study procedures will be reviewed with the participant, and written consent will be obtained upon arrival during this visit.

Upon successfully completing the screening evaluations, all eligible subjects will complete 7 total study visits (of which some may be spread over multiple days), 5 of which will be test visits involving the administration of CVL-562 or placebo (Figure 1). Each test visit will be separated by at least 48 hours (six half-lives of CVL-562, per investigator brochure from Pfizer/Cerevel the half-life is 7.5 hours). Given the repeated visits required in this study, participants will be offered an elective inpatient admission on a research psychiatric unit, if space is available, for further observation or isolation (due to COVID-19 exposure risk) as needed. For those requiring housing, a stay at a nearby hotel will be offered. The baseline visit will involve informed consent and screening assessments to determine eligibility, including a structured clinical interview (SCID-V), Penn Reading Assessment (PRA), Edinburgh Handedness Inventory, PANSS, PennCNB letter n-back task, Calgary Depression Scale for Schizophrenia, spatial working

memory task, practice flashing checkerboard task, Beck Anxiety Inventory, Columbia-Suicide Severity Rating Scale—baseline/screening (C-SSRS, baseline/screening), urine toxicology/pregnancy, baseline bloodwork (complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), Hepatitis B, Hepatitis C, HIV, genetics (optional)), EKG, vital signs, health history, physical exam, assessment and an optional mock scanner experience. Pre-existing health information may be used to determine eligibility if it was obtained within 3 weeks prior to the date of consent. Subjects will be randomized to the order of doses of CVL-562 (1 mg, 4 mg, 15 mg, or 25 mg, immediate release formulation) or placebo for the next 5 visits. The randomization will assign 75% of patients to the highest dose on the last visit and 25% will receive the highest dose on one of the other four visits. Only the highest dose will be subject to this pseudo-randomization strategy. This is intended to minimize the impact on study completion of the association of the 25 mg dose with nausea in approximately 30% of subjects, which might unblind subjects and lead to study discontinuation. All other dosing will be randomly distributed. All female participants will be required to be on birth control (or abstinence) and will receive pregnancy tests at the start of each study visit. Information on nicotine use, the amount and duration of use will be collected at the start of the study using the Fagerstrom Test for Nicotine Dependence Questionnaire. All subjects will be tested for COVID-19 as part of Visit 1. COVID-19 testing may be repeated after Visit 1 based on symptoms.

Each treatment visit will begin with clinical assessments required to continue on this study. These assessments include urine sample for toxicology/pregnancy exam, Positive and Negative Syndrome Scale (PANSS), Columbia-Suicide Severity Rating Scale—since last visit (C-SSRS, since last visit), MRI safety assessment, and vital signs. A lifestyle questionnaire will be administered to understand basic events that occurred in the hours before the scan, including how much caffeine was used, how much food was eaten, pain levels and whether nicotine was used. If participants have not had a meal within two hours prior to the start of the study visit, they will be offered a small meal to induce a fed state, as the timing of the study drug's effects have a different timeline during a fed vs. fasting state. A brief refresher session on the spatial working memory task will be presented to the participants to remind them of the task instructions, at this point or after drug administration prior to the start of scanning. Following this, the treatment visit medication will be administered and the subject will enter the fMRI scanner to perform the spatial working memory task. Vital signs will be taken before drug administration and prior to and after scanning. Scanning will be timed to have imaging coincide with peak CVL-562 plasma levels, i.e., it will begin approximately 75 minutes following medication administration and last for approximately 90 minutes (up to 2 hours). Plasma levels of CVL-562 will be obtained prior to and following imaging with a blood draw from either venipuncture or an IV continued with a slow rate of normal saline infused during the scan (20 mL/hour) to minimize needlesticks. The slow rate of normal saline is used to keep the IV open during the scan, and prevent clotting in the IV. The use of either two

venipunctures (one prior to imaging and one following imaging) or a continuous IV will be made after assessing patient preference, and procedure feasibility. Vital signs, PANSS, C-SSRS—since last visit, and PennCNB will be administered immediately following removal from the scanner. All subjects will be observed for at least 2 hours following dosing, and provided follow-up (see below, Protection Against CVL-562 Risks).

After completion of the 5 treatment visits, participants will be scheduled for a follow-up visit to conduct an exit interview, with debriefing of the study.

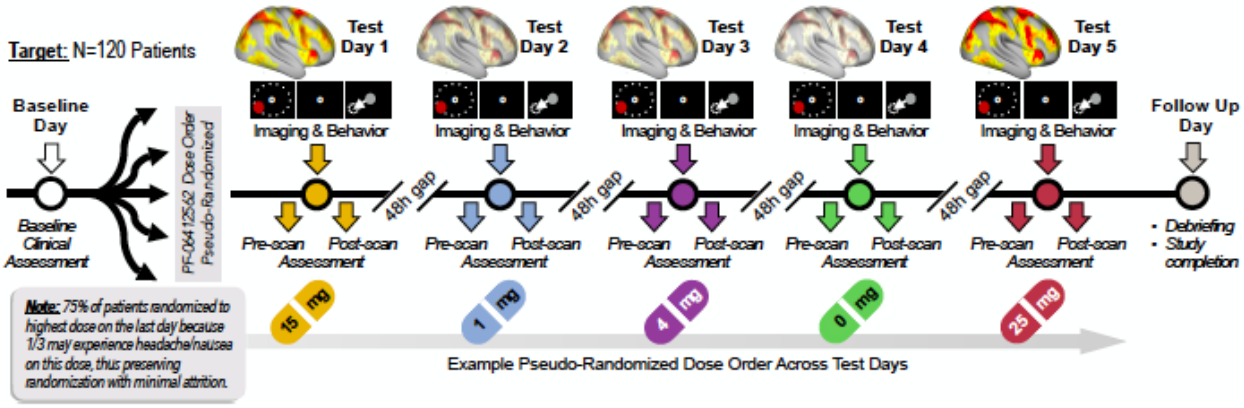

Figure 1. Overview of Study Design.

4.1.1 4.1.1. Protection Against CVL-562 Risks.

The subject recruitment process entails an effective and rigorous screening, which will exclude any subjects who could be at greater risk for complications because of medical, neurological or psychiatric illnesses. We have successfully employed these stringent screening procedures in all our protocols and have had great success in recruiting subjects who are at low risk for receiving experimental pharmacology (ex: ketamine (55), delta9-tetrahydrocannabinol (43, 56), etc.) and who are likely to tolerate the procedure well. Subjects will be monitored during drug administration by an experienced member of the research team (nurse, coordinator and/or psychiatrist). These team members have experience with pharmacologic imaging, and will provide ongoing support and alleviate concerns for those subjects experiencing side-effects. Furthermore, ondansetron will be available for intravenous or sublingual administration to rapidly control nausea and/or vomiting during scanning if needed. Subjects will be observed for at least 2 hours after dosing. If intolerable physical or behavioral symptoms persist, subjects will be assessed in the emergency room and/or on an inpatient unit depending on the level of severity of symptoms for further observation and overnight, if necessary. Vitals will be assessed prior to drug administration on each test visit, just prior to beginning fMRI scan, and after fMRI scanning finishes. We will also administer the Columbia-Suicide Severity Rating Scale—since last visit (C-SSRS, since last visit) prior to drug administration and after fMRI scanning, though it is important to note that CVL-562 has no known effect on suicidality. Subjects will be

advised NOT to drive to and from the testing sessions, and instead we will arrange alternative means of transportation for all subjects (e.g. taxi). A physician investigator (MD) will approve the discharge of subjects following the completion of each treatment visit. Following discharge from each treatment visit, subjects will be provided a number to call to reach an on-call psychiatrist (24 hours/day) should delayed unpleasant effects occur. Subjects who experience any intolerable effects at any point will not be permitted to continue participation. Please see Section 9.**4** for further details on criteria for stopping participation. Post-testing: Contact with participants will be maintained during the study and following its completion. We will contact all subjects approximately 24 hours after drug administration to check for side effects. A final, in-person follow-up visit will occur after the last treatment visit to assess side effects and complete final bloodwork. Furthermore, we will conduct a follow-up call approximately 1 month after study completion (i.e., after the final in-person visit) to assess for late or ongoing adverse effects. Any subjects that experience lingering side effects will be followed by the study team until resolved or stabilized, and then will be directed to follow-up with their primary health care provider. All imaging will occur at sites specifically designed, equipped, and functioning in support of these types of studies, and includes the onsite presence of medical supervision with experienced medical, nursing, research and/or technical staff. Although we do not expect significant problems to occur, if any adverse effects occur during the fMRI session, appropriate treatment will be instituted for symptomatic relief. All sites will implement clear protocols for addressing medical urgencies and emergencies, including, but not limited to, emergent assessment, use of a crash cart, and transportation to the emergency room.

4.2 Treatment Regimen

The clinical trial is designed as a multi-center, single, randomized dosing, double-blind study with 5 treatment visits, each visit start time separated by at least 48 hours (6 half-lives of CVL-562). We aim to complete all in-person visits for each participant over approximately a 1-2 month period, with likely variation given patient availability and schedule. Below is a more detailed description of procedures.

4.2.1 Clinical Protocol Schedule of Events Completed by an Individual

- Pre-screening - Potential participants will be contacted by phone by a research staff member to determine whether a participant is eligible to participate in an in-person screening visit (baseline visit). The data indicating that a participant is found to be eligible for Visit 1 will be entered directly into a REDCap database. Those who fail to meet eligibility criteria on the phone screen will not be invited to the in-person screening/baseline visit and will not participate in any additional research procedures. Potential participants will then be invited for the baseline visit (in-person assessment) with a doctoral-level clinician or an appropriately trained senior research assistant. Given the longitudinal

nature of the study, as well as planning for attrition, we aim to recruit a total of 120 participants who would be eligible to receive CVL-562 based on medical and psychiatric assessments. Of those, we aim to have 100 participants complete full procedures (we have estimated attrition of 20 participants). The number of participants who are consented may exceed 120 subjects as we anticipate that some will be found ineligible on the first baseline visit due to medical or psychiatric or other reasons.

- Visit 1 - This visit will serve as a baseline pre-randomization visit (4-8 hours total, possibly spread across a few days). During this visit, we will obtain informed consent and ascertain full eligibility criteria. The baseline visit will involve a structured clinical interview (SCID-V), Penn Reading Assessment (PRA), Edinburgh Handedness Inventory, spatial working memory task, practice flashing checkerboard task, PANSS, PennCNB letter n-back task, Calgary Depression Scale for Schizophrenia, Beck Anxiety Inventory, Columbia-Suicide Severity Rating Scale—baseline/screening (C-SSRS, baseline/screening), urine toxicology/pregnancy, baseline bloodwork (complete blood count with differential, comprehensive metabolic panel, Hepatitis B, Hepatitis C, HIV; optional genetics), EKG, vital signs, health history, physical exam, MRI eligibility, and an optional mock scanner experience. Pre-existing health information may be used to determine eligibility if it was obtained within 3 weeks prior to the date of consent. All subjects will be tested for COVID-19 as part of Visit 1. COVID-19 testing may be repeated after Visit 1 based on symptoms. All participants will be consented to participate in these procedures, however, only those who are found eligible for test visits will continue with the study. Given the numerous assessments and the length of time to complete them, the practical difficulties in securing MRI scan time, patient availability, and the need to keep patients engaged during the study to minimize dropout, this first visit may be split into a few days within the window of consent and Visit 2 (8 weeks). Following the end of Visit 1, the clinical lead investigator at each site will assess and confirm eligibility for further study visits based on information gathered at that visit and inclusion/exclusion criteria. For those participants for whom eligibility is difficult to determine, they will be discussed with a larger group of investigators to reach consensus on eligibility. Following determination of eligibility for test visits, participants will be randomized to a dosing schedule as follows: placebo, 1 mg, 4 mg, 15 mg, or 25 mg —75% of the patients will be randomized to get the highest dose on the last visit.

- Visit 2 - Test visit (4-6 hours): Initial clinical assessments including urine sample for toxicology/pregnancy exam, PANSS, vital signs, Columbia-Suicide Severity Rating Scale—since last visit (C-SSRS, since last visit), MRI safety assessment. A lifestyle questionnaire will be administered to understand basic events that occurred in the hours before the scan, including how much caffeine was used, how much food was eaten, pain levels and whether nicotine was used. If participants have not had a meal within 2 hours prior to

the start of the study visit, they will be offered a small meal to induce a fed state, as the effects of the study drug have a different timing during a fed vs. fasting state. A brief refresher session on the spatial working memory task and the flashing checkerboard task will be presented to the participants to remind them of the task instructions, at this point or after drug administration prior to the start of scanning. Following this, the treatment visit medication will be administered. Then, the subject will have vital signs re-checked after medication administration, and enter the fMRI scanner to complete approximately 90 minutes (up to 2 hours) of data collection. Data collected in the scanner includes both high-resolution T1-weighted and T2-weighted structural images (approximately 20 minutes), 4 multi-band functional BOLD runs that involve trials of spatial working memory, trials of motor control, and trials of spatial working memory with distraction (approximately 40 minutes total), resting state scan (approximately 10 minutes), a resting state arterial spin labeling (ASL) scan to assess for changes in cerebral blood flow (approximately 10 minutes), and brief visual checkboard stimuli (to explore neurovascular coupling effects of CVL-562; approximately 5 min). The first test visit will also include a diffusion-weighted image (DWI) (approximately 20 minutes). If the DWI is not collected at the first test visit it will be collected on one of the subsequent test visits. Plasma levels of CVL-562 will be obtained prior to and following imaging with a blood draw from either venipuncture or an IV continued with a slow rate of normal saline infused during the scan (20 mL/hour) to minimize needlesticks. The slow rate of normal saline is used to keep the IV open during the scan, and prevent clotting in the IV. The use of either two venipunctures (one prior to imaging and one following imaging) or a continuous IV will be made after assessing patient preference, and procedure feasibility. Vital signs, PANSS, Columbia-Suicide Severity Rating Scale—since last visit (C-SSRS, since last visit), and PennCNB battery will be administered immediately after the completion of the scan. A study physician will be available for the entire test visit. Subjects will be observed for at least 2 hours following dose administration, and provided follow-up. Visits 3, 4, 5, 6 will be identical to Visit 2, with at least 48 hours of separation (six half-lives of CVL-562) between the start of each test visit day. All participants will be contacted by phone approximately 24 hours after the visit to briefly assess for any adverse effects. COVID-19 testing may be done if symptoms are suspected.

- Visits 3, 4, 5, 6 - all identical to Visit 2.

- Visit 7 - Follow up visit (approximately 2 hours): Individual follow up and de-briefing. At this time female participants will receive a final urine pregnancy test. All participants will have a final blood draw for labwork for safety monitoring (complete blood count (CBC) with differential, and complete metabolic profile (CMP)). All participants will be called approximately 1 month after this follow up visit to assess for long-term effects

4.3 Special Procedures Related to COVID-19

Given the ongoing pandemic, and the shifting waves of illness that have ensued since this protocol was approved, there will be additional precautions to ensure the safety of the participant and the staff during the course of the study and pandemic. All sites will follow their required site procedures for cleaning, distancing and testing. During Visit 1, all participants will receive COVID-19 testing. If a participant tests positive, they will be removed from study procedures and asked to follow current CDC guidelines for isolation and further testing. If, after the isolation period, they do not develop symptoms, they will be evaluated for continuation in the study. If they become symptomatic, the severity of their illness will be evaluated for potential exclusion from the study. As the exclusion criterion includes unstable medical illnesses, those participants who are COVID-19 positive and have significant symptoms may be excluded under this criterion. Should symptoms develop during the course of the study, participants will be tested for COVID-19. The severity of their symptoms, in conjunction with the outcome of testing, will be assessed for possible exclusion from the study, as determined by the clinical lead investigator at each site. Those who recover from their symptoms and are willing to resume study procedures must be free of significant symptoms at the time of restarting study procedures. Those who test positive for COVID-19 during this study will be designated as such for purposes of exploratory data analyses.

Study procedures will generally continue to be on-site; however, to minimize contact, some assessments for Visit 1 may be conducted or monitored virtually, at the discretion of the site PI and research staff and based on the needs of the participant and local site. These assessments may include clinical interviews, scales, questionnaires, and the PRA. The sWM and Flashing Checkerboard task practices and medical assessments will continue to be done in-person. For the virtual components, study participants will be instructed to participate virtually in the same way they would while onsite (ex: alone in a room, no distractions, available for the designated amount of time).

All virtual assessments will be conducted using secure, password-protected, HIPAA-compliant videoconferencing platform. Conducting these assessments virtually will allow research staff to continue research, maintain social distance, and also observe necessary components of affect (facial expression, vocal quality) that would be difficult to do behind masks. Finally, to ensure that assessment scoring can be reliable, we will record interviews, which may be an optional part of the study. Recording will allow investigators to ensure reliability and accuracy of data collection while conducting assessments virtually. Consenting for recording of assessments will be optional for participation in the study. All recordings will be stored centrally at Yale using a secure, password-protected HIPAA-compliant platform and each site will keep a copy of their recordings in a secure, password-protected HIPAA-compliant platform. Only trained research staff members and investigators will have access to these videos for the purposes of assessing the reliability and accuracy of these assessments. Study processes may continue to

be modified in response to the COVID-19 pandemic, as medical and public health considerations evolve.

4.4 Randomization

Patients will each have 5 treatment visits, and the order of placebo, 1 mg, 4 mg, 15 mg or 25 mg dosing will be randomized through the Investigational Drug Services at Yale New Haven Hospital. Drug dosing schedules will be balanced within and across sites. Each treatment visit start time would be separated by >=48 hours (6 half-lives of CVL-562). The randomization will assign 75% of patients to the highest dose on the last visit and 25% will receive the highest dose on one of the other four visits. Only the highest dose will be subject to this pseudo-randomization strategy, and all other doses will be randomly distributed. This randomization strategy is intended to minimize the impact on study completion of the association of the 25 mg dose with nausea in approximately 30% of subjects, which might unblind subjects and lead to study discontinuation. Patients and investigators will be blind to the randomization. Cerevel will distribute the drug to the Yale Pharmacy directly. Yale Pharmacy will then distribute the drug in kits determined in the randomization protocol.

4.5 Side Effect Profiles from Prior Studies

Prior studies have been conducted using maximum doses in excess of what is described here. Overall, prior human studies find the study drug to be safe and well tolerated. The most common adverse events are nausea and headache, and these appear to be dose-dependent. In all studies, no deaths have occurred, and no significant changes in EKG, or bloodwork have occurred. See below (Table 1) for a description of prior studies conducted in human subjects. As we use a lower maximum dose than prior human studies and use four single doses separated by at least 48 hours rather than repeated daily doses for 15 days used in the prior schizophrenia study, we expect the frequency of side effects to be even lower in the proposed studies.

Study	Participants	Study Design	Dosing	Adverse Events
B7441001	39 healthy adults	Ascending, single-dose first in human study	0.5 - 20 mg single dosing	Nausea, vomiting, headache, somnolence; most mild/mod severity
B7441002	40 healthy adults	investigator/subject-blind, placebo controlled, multiple-dose escalation study	3 mg three times daily - 25 mg three times daily	Nausea, vomiting, headache and abdominal discomfort
B7441003	13 patients with Parkinson's Disease	Randomized, investigator/subject blind, sponsor-open placebo controlled crossover study to test motor effects	Split dosing of 30 mg + 20 mg 4 hours later	Nausea, fatigue, vomiting, anxiety, constipation
B7441005	5 healthy adults	PET scan with SCH-23390 (D1-ligand)	30 mg single dose	Nausea, vomiting
B7441006	12 healthy adults	Open label, single dose crossover study to examine metabolite and modified release (MR) formulation	3 mg - 30 mg single dose of MR	Headache
B7441004	77 healthy adults	Randomized, double-blind, placebo controlled study to test effects on cognition in those with low WM	3 mg twice daily or 15 mg twice daily, both MR	Headache, nausea; 1 drop-out from orthostatic heart rate
B7441007	103 patients with schizophrenia	Randomized, double-blind, placebo controlled, parallel-group study to test effects on cognition and motivation	3 mg twice daily, 9 mg twice daily or 45 mg twice daily IR x 15 days	Headache, nausea; 1 worsened psychosis (3 mg twice daily)
Proposed Study	100 patients with schizophrenia (120 recruited)	Randomly assigned, single dose study to test effects on cognitive neural circuits	placebo, 1 mg, 4 mg, 15 mg, and 25 mg IR single dosing	

Table 1. Prior human studies using CVL-562.

5. CONCOMITANT MEDICATIONS

Participants may continue to be treated with psychiatric and medical medications as long as dosing has been stable for 3 weeks. As stated earlier, we limit antipsychotics allowed in the study to agents with low D1R affinity, thereby excluding olanzapine, clozapine, ziprasidone and asenapine.

CVL-562, as well as some of the allowable antipsychotics in this study are metabolized by the P450 enzyme, CYP3A4. Therefore, both strong and moderate inducers (eg, carbamazepine) and inhibitors (eg, ketoconazole, valproate) of CYP3A4 are excluded during this study, as well as the 10 days prior to the initial visit.

5.1 Diet and Other Considerations

As CVL-562 is metabolized by the P450 enzyme, CYP3A4 (Investigator Brochure), both strong and moderate inducers (carbamazepine) and inhibitors (ketoconazole, valproate, etc., as well as grapefruit juice (an inhibitor of CYP3A4) will be excluded during this study, as well as the 10 days prior to the initial visit.

In relation to MRI scanning, information on participant caffeine use and nicotine use will be collected in order to assess possible confounds on the BOLD signal.

5.2 Rescue Medication and Supportive Care

There is no rescue medication that reverses the effects of CVL-562. Intravenous or sublingual ondansetron will be available to treat acute nausea/vomiting that may occur on test days after the administration of CVL-562. For acute anxiety related to procedures in the scanner, participants will be removed from the scanner and assessed for continuation in the study.

6. PATIENT POPULATION

Patients with schizophrenia, schizoaffective or schizophreniform disorder participating in this study will be recruited primarily from specialized resources at each site dedicated to the early identification and treatment of patients with psychosis. The recruitment from these programs would be supplemented by referrals from established ambulatory clinics, intensive outpatient programs, inpatient units, and emergency room (ER) settings. In addition, clinically-based recruitment may occur through chart reviews and cold calling via telephone calls. Therefore, much of the communication strategies for identifying and soliciting referrals are related to communicating with specific relevant sources at each site. Nonetheless, we will use a variety of public sources (radio, newspaper, advertisement on public buses, Craigslist, etc.) to ensure a steady flow of patients at each site. In doing so, recruitment will employ an established pipeline that we and our colleagues across the Consortium sites have developed over the years. Subjects will be recruited through a combination of print, on-line, and traditional media advertising, posting of flyers in the local community, and outreach to community clinicians. All advertising materials will be approved in advance by the Institutional Review Board. Potential subjects will be instructed to contact the clinic coordinator(s) online or by phone to schedule a time to complete the initial phone screen (described earlier).

6.1 Inclusion Criteria

- Between the ages of 18 (including 18 years of age) and 45 (up to 45 years and 11 months) at the time of baseline study visit.
- Able to provide informed consent (as established by consent interview), and voluntary, signed informed consent prior to the performance of any study-specific procedures
- Willing and able to perform study-relevant clinical assessments and Magnetic Resonance Imaging (MRI) as assessed by research staff.
- Meet Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder on the basis of the Structured Clinical Interview for DSM-5 (SCID-5).
- Be within 10 years of the onset of psychosis based on clinical assessment at the time of Visit 1.
- Treatment seeking and willing to accept the constraints on treatment entailed by the study.

- Able to demonstrate a basic ability to follow spatial working memory task instructions and perform necessary related motor functions.
- Demonstrate a premorbid IQ of ≥80 based on the Penn Reading Assessment (PRA) (1). The PRA correlates with other measures of IQ including the Wide Range Achievement Test (WRAT), but is computerized, based in the laboratory of co-investigators Ruben C. Gur and Raquel E. Gur, and brief to administer, allowing us to lessen the assessment burden on an already lengthy first visit.
- Be fluent in English as assessed by research staff.
- Clinically stable treatment for at least two months prior to Visit 1 (no hospitalizations, or current suicidal/homicidal active ideation, intent, or plan).
- On a stable psychotropic medication regimen (can include no psychotropic medications) for at least 3 weeks prior to Visit 1, and willing to maintain an unchanged regimen during the study. If on depot antipsychotics, participants must have stable dosing for at least two consecutive injections (including the most recent one) as the most recent injections. If on Invega Trinza, there must be no plans to change dosing during the course of the study.
- For women of child bearing potential, no intention to become pregnant during the study period, and agreement to use a reliable method of birth control (e.g. Intra-Uterine Device (IUD), hormonal contraception, abstinence, condoms) during the study period. Women will be asked to continue their method of contraception for 1 month after receiving their final dose of medication. Any individual who becomes pregnant during the study will be immediately removed, and discussion of the risks and benefits of ongoing pharmacotherapy will proceed on purely clinical grounds.

6.2 Exclusion Criteria

- Any unstable medical, psychiatric, or neurological condition (including active or otherwise remarkable suicidal or homicidal ideation) that may necessitate urgent treatment. Active medical conditions that are minor or well controlled are not exclusionary if they do not affect risk to the patient, metabolism of study drug, or the study results (e.g. well-controlled type II diabetes or hypertension) as per the judgment of the investigator.
- Be currently treated with any of the following: olanzapine, clozapine, ziprasidone or asenapine, in order to avoid prominent D1 receptor effects.
- Any major neurological disease, brain injury, epilepsy, or history of severe head trauma, including concussion with loss of consciousness greater than or equal to > 15 minutes, or of psychosurgery.
- History of significant cardiac disease (ex: ischemia, arrhythmia).
- Any clinically significant abnormality on baseline medical screening tests (electrocardiogram (EKG), complete blood count with differential (CBC), complete metabolic profile (CMP).
- Hepatitis B or C (by report or testing) in the presence of abnormal liver function tests
- Human Immunodeficiency Virus (HIV) or Acquired Immune Deficiency

Syndrome (AIDS) (by report or by testing) due cognitive effects of HIV and AIDS.
- Baseline EKG showing prolonged QTc interval (>450 for males, >470 for females, Framingham correction(3)), with repeat measurement showing the same abnormality.
- Current mood episode meeting criteria for a major depressive episode or a manic or hypomanic episode.
- History of electroconvulsive therapy (ECT) or treatment with neurostimulation in the past 6 months, or with plans to begin either such treatment during the study.
- History of ADHD pre-morbid to the onset of psychosis or other psychiatric illnesses that may be accompanied by cognitive impairments.
- Meeting SCID-5 moderate or severe substance use disorder for any substance other than nicotine within the 3 months prior to the initial assessment.
- Positive urine toxicology testing for any substance other than marijuana or those prescribed for medical reasons Pregnancy or intention to become pregnant during the study.
- Lactating/breast-feeding or intending to do so during the study
- Any non-MRI compatible metal in the body or other contraindication to MR imaging. A copper IUD is allowable if permitted by local MRI practices.
- Severe claustrophobia, back pain, morbid obesity, or other condition that may make an extended MR session difficult or lead to excessive movement during the imaging session.
- Color blindness, strabismus or other uncorrectable visual problems. Those wearing glasses would be asked to use MRI-safe glasses.
- Daily use of the following medication within for at least 10 days prior to the initial visit study or during the study: Long-acting nighttime or daytime gamma aminobutyric acid-A (GABA-A) receptor facilitators; anticonvulsant medications used at high doses or for seizure control, or psychostimulants or medical cannabis. Participants can be re-assessed for eligibility once they have been free of daily use of these medications for >10 days. Participants may take non-GABAergic sleep medications, short-acting GABA receptor facilitators (benzodiazepine, non-benzodiazepine) prior to and during the study.
- Any change in type or dose of psychotropic medications within 3 weeks prior to initial visit or during study to avoid transient effects of medication regimen change. Medication type and dose will be carefully recorded and used as a covariate in analyses. Participants can be re-assessed for eligibility once they have been on a stable dose of medication for >3 weeks.
- CVL-562 is metabolized by P450 CYP3A4. In order to avoid pharmacokinetic interactions, medications or substances that induce (barbiturate, carbamazepine, etc.) or are moderate-strong inhibitors (ketoconazole, etc.; grapefruit juice) are excluded if used within 10 days prior to or during study. Participants can be re-assessed for eligibility once they have been free of these medications/substances for >10 days.
- Active attempts to discontinue smoking, vaping or other nicotine products within the 3 weeks prior to study or during the study. Participants can be re-

assessed once quit attempt is stable.
- Diastolic blood pressure >95 or <50 mmHg or systolic blood pressure > 170 or <80 mmHg with repeat measurement showing the same abnormality.
- History of allergy or other contraindication to the proposed pharmacotherapy.
- Other medication treatment with which proposed pharmacotherapy is contraindicated, in the opinion of study psychiatrists or of a subject's prescribing psychiatrist.

7. DESCRIPTION OF PROCEDURES

7.1 Study Entry / Registration

Eligibility will be determined locally by the site PI and/or research team using an eligibility checklist. The participant will be assigned a unique study ID generated by the NIMH Data Archive (NDA), pseudo-GUID (PGUID), after screening. A list of NIH PGUIDs will be provided to each site at start-up and assigned to each enrolled participant consecutively. The NIH PGUID will be used when the participant is registered into REDCap and will be used in related study documents and data collection. Because the NIH PGUIDs are lengthy but useful for public data upload through the National Institute of Mental Health Data Archive (NDA), a shorter, Simple ID will be used for the purposes of labeling the investigational drug packets and other data that require shorter identifiers. The corresponding Simple ID will be also entered into REDCap. Subjects will be entered into REDCap by research staff. Allocation of patients to treatment groups will be done using the randomization process outlined in section 4.3 Randomization. De-identified data will be made publicly available through the NDA with data uploaded every 6 months.

Participant re-screening may occur when a participant's ability to meet inclusion or exclusion criteria has changed to suggest potential eligibility, when participants resume contact with the study team after being lost to follow-up, or when participants express renewed interest in participating after previously declining further participation. During re-screening, all study procedures should be repeated except for the SCID-V, the PRA and Edinburgh Handedness Inventory.

7.2 Safety and Data Capture of Laboratory Procedures and Assessments

7.2.1 Psychological Assessments

These are non-invasive assessments and have been used without difficulty or adverse events in previous studies with a similar population and design. Patients will be offered the opportunity to take frequent breaks to minimize fatigue. There are potential risks that subjects may become uncomfortable or distressed when discussing personal issues with study personnel or treatment providers. All participants are welcome to withdraw from the study at any time. Inter-rater reliability will be assessed. For all assessments with electronic source capture, a

paper source will be used as a backup option in the event of technical glitches or technical unavailability. The data from the paper source will then be manually entered by staff into REDCap and noted as coming from a paper source. The following assessments will be administered:

- **Structured Clinical Interview for DSM-V (SCID-V)(57)—**this is a structured clinical interview that assesses psychiatric symptomatology and psychiatric diagnoses. All criteria are based on the DSM-V. Source data will be captured in electronic format through NetSCID's via Telesage and exported and entered into REDCap.
- **Spatial working memory task(21)**—this is a computerized fMRI task that tests participant's working memory for spatial locations. Participants are asked to remember the location of a circle on each trial, and they use a high-precision joystick to indicate where they best remember the location to be. The control trials involve no working memory and involve moving the joystick to the location of the circle that is presented onscreen. On some trials, a second circle in a different location (noted as a distractor—placed either near to, or far from, the original circle) will be presented as a distractor to test the stability of the working memory. Participants will be trained on this task at the initial visit. At each subsequent test visit, they will perform this task in the fMRI scanner after receiving a dose of drug. Behavioral source data will be from E-Prime Eyelink SR Research software and Biopac or Siemens Physiological Measurement Unit and analyzed in R. Imaging data will be collected at the scanner, and centrally stored using support from XNAT software maintained by investigators at Yale University. Behavioral and physiological data collected during the fMRI scan will be centrally stored at Yale University. Participants will also complete a version of this task at the baseline visit outside of the scanner in order to become familiar with this task and its instructions.
- **Flashing Checkerboard Task(58)—**This is a computerized fMRI task used to measure neurovascular coupling. Participants are asked to view a flashing checkerboard and press a button when the flashing stops. As with the spatial working memory task, the imaging data will be collected at the scanner and centrally stored using support from XNAT software maintained by investigators at Yale University. Behavioral data collected during the fMRI scan will be centrally stored at Yale University. Participants will also complete a practice session at Visit 1, and a few brief trials before the scan to become familiar with the instructions.
- **The Positive and Negative Syndrome Scale (PANSS)(59, 60)—**this is a structured clinical interview that assesses symptoms of psychotic illnesses. Source data will be captured in electronic forms in REDCap.
- **Penn Computerized Neurocognitive Battery (PennCNB)(61)—**this is a standardized battery of cognitive tests on the computer that assesses aspects of short-term memory, working memory, executive

function, etc. Data are captured and stored in a centralized database managed by the investigators at the University of Pennsylvania. The PennCNB n-back letter task, which assesses working memory and will be used in Visit 1, is part of the PennCNB.

- **Penn Reading Assessment (PRA)(1)**—this is an assessment designed, validated and published by the investigators at the University of Pennsylvania to assess premorbid IQ. This is computerized and data are captured and stored in a centralized database managed by the investigators at the University of Pennsylvania.
- **Fagerstrom Test for Nicotine Dependence (FTND)(62)**—this is a questionnaire administered by research staff to assess nicotine use. This scale has been made in the Redcap system and source data will be electronic in the REDCap system.
- **Calgary Depression Scale for Schizophrenia(63)**—this is a rating scale administered by research staff to assess depression symptoms in patients with psychotic illnesses. This scale has been made in the REDCap system and source data will be electronic in the REDCap system.
- **Beck Anxiety Inventory(64)**—this is a rating scale to assess symptoms of anxiety and is completed by the participant. This scale has been made in the Redcap system and source data will be electronic in the REDCap system.
- **Columbia-Suicide Severity Rating Scale—baseline/screening (C-SSRS, baseline/screening)(65)**—this is a structured interview administered by research staff to assess suicidality and related behaviors. This scale has been made in the REDCap system and source data will be electronic in the REDCap system.
- **Columbia-Suicide Severity Rating Scale—since last visit (C-SSRS, since last visit)(65)**—this is a structured interview administered by research staff to assess suicidality and related behaviors since the last time the scale was administered. This will help us track any changes to suicidality and related behaviors during the course of the study. This scale has been made in the Redcap system and source data will be electronic in the REDCap system.
- **Edinburgh Handedness Inventory**(66)—this is a rating scale to assess hand dominance and completed by the participant. The scale has been made in the REDCap system, and source data will be electronic in the REDCap system.
- **Lifestyle Questionnaire**—this is a structured interview to assess events that occur on the day of scanning prior to the fMRI scan being obtained. This covers information such as caffeine use, food intake and hydration. The source data is electronic and this information will be entered directly into REDCap.

7.2.2 Functional magnetic resonance imaging (fMRI).

It is important to note that research has not found any adverse side-effects of MR imaging at field strengths used in the present protocol. fMRI scans will be gathered according to the United States Food and Drug Administration (FDA) guidelines for magnet strength and exposure to radio waves. Subjects will be monitored closely throughout the scan. Some subjects feel uncomfortable or anxious and on rare occasions, subjects experience upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. There are some risks with an MRI scan for certain people, if subjects have a pacemaker or some metal object inside their body for example, however, we will take exceptional precautions through an extensive MR safety screen to exclude subjects with any contraindications during initial screening (MRI safety assessment—site specific). Furthermore, we will exclude any individuals who express concern about small spaces/claustrophobia during screening. For those subjects participating in the study we will offer the optional opportunity to undergo an adaptation session in a mock scanner to provide subjects an opportunity to be familiar with lying in the MRI scanner. If a participant becomes anxious during scanning, we will initially try to relax them by speaking to them over the intercom. In our experience, participants are the most uncomfortable when first entering the magnet, and the feelings dissipate as people adapt to the situation. If the discomfort persists, or if at any time a participant requests so, we will stop the imaging session immediately. Further continuation of this participant in the remainder of the study will be determined by the study investigators in collaboration with the participant.

7.2.3 Urine drug screen

The following drugs of abuse will be screened for: cannabinoids, cocaine, opiates, amphetamines, methamphetamines, benzodiazepines, barbiturates, and phencyclidine. If a participant tests positive for any drug of abuse except for marijuana or those prescribed for medical reasons on the urine drug test during Visits 1-6, they will not be allowed to continue further in the study, but will have the opportunity to continue once they abstain and the urine drug test is negative for those substances. Once the urine drug test is negative, the participant may be re-evaluated to continue in the study. If the participant declines to abstain, they will be excluded from the study.

If a participant tests positive for marijuana use at Visit 1, but their urine THC level is <150 ng/mL, they will be allowed to participate in the study. Marijuana use is very common in patients with schizophrenia, particularly those who are younger. This cutoff will allow us to recruit a wider group of early-episode patients with schizophrenia with presumed recreational marijuana use, but still exclude those with heavy use. Furthermore, we will continue to measure urine THC at Visits 2-6, and use the results as a covariate in analysis. The source data will be lab reports, and electronic capture into REDCap.

7.2.4 **Physiological measures**

Physiological measures including blood pressure, respiratory rate and heart rate will be obtained at each visit. Vitals signs for Visit 1 may be considered relevant for up to 8 weeks after being measured. On test visits, this information will be obtained prior to drug administration, after drug administration but before fMRI scanning, and after completion of fMRI scanning. Prior to dosing the drug on Visits 2-6, if vital signs are repeatedly out of range based on our designated inclusion/exclusion criteria, we will hold the study drug that day and, we will re-check the vital signs at the subsequent visit. This information will be entered into REDCap. Continuous physiological (respiratory rate and heart rate) information will also be collected during the fMRI scan itself using MRI safe equipment from either the Siemens Physiological Measurement Unit or Biopac for potential exploratory regression analyses of the neuroimaging data. This information will be collected in electronic format by the respective equipment and stored centrally at Yale University.

7.2.5 12-lead electrocardiogram

A standard resting, 12-lead electrocardiogram (EKG) will be obtained, and be documented by recording date, time, normal/abnormal, abnormality (if any), and if clinically significant. A pre-existing EKG may be used to determine eligibility if it was obtained within 3 weeks prior to the date of consent.

All EKGs will be evaluated by the investigators or a qualified cardiologist. If indicated, additional EKG assessments will be made at the discretion of the investigator. A cardiologist will rate the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. Those with prolonged QTc seen on EKG (>450 ms for males; >470 ms for females) will be excluded. EKG data will be uploaded into REDCap. The EKG may be considered relevant for up to 8 weeks after collected (11 weeks if obtained within the 3 weeks prior to the date of consent).

7.2.6 Physical examination and health history

The physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen, and neurological systems. Health history assessment will include personal and family health history. All physical exam and health history documentation will be directly captured using REDCap. For participants who have lapses in study participation at Visit 1, the physical exam and health history may be considered relevant for up to 8 weeks after they were conducted. A pre-existing physical examination and health history may be used to determine eligibility if it was obtained within 3 weeks prior to the date of consent.

7.2.7 Laboratory assessments

Blood samples for determination of clinical chemistry and hematology parameters will be taken at the time of the baseline visit and at the final visit (Table 2). For participants who have lapses in study participation at Visit 1, medical lab assessments may be considered relevant for up to 8 weeks from collection (up to 11 weeks if it was obtained 3 weeks prior to the date of consent.). Pre-existing labwork may be used to determine eligibility if it was obtained within 3 weeks prior to the date of consent. Source data will be the lab reports, and the data will be entered into REDCap. Date and time of collection and results will be recorded. Collecting bloodwork for genetics will be optional on the part of the participant. The use of the genetic materials will be exploratory and used in relation to imaging and treatment findings. All blood collected for genetics analysis will be stored at Yale University, the site of the Principal Investigator. Any extracted genetic data will then be made available through the National Institutes of Health database of Genotypes and Phenotypes (daGaP). The following laboratory variables will be measured:

Hematology	**Infectious Disease**	**Clinical Chemistry**	**Urine**
Complete Blood Count (CBC) with Differential	Hepatitis B panel (Hep B surface antigen, surface antibody and core antibody)	Comprehensive Metabolic Profile (CMP)	Toxicology
	Hepatitis C (antibody)		Pregnancy (hcG)
	HIV		

Table 3. Laboratory Assessments. Positive results for reportable communicable diseases will be reported to the public health authority as required by state law. The reportable diseases include HIV, Hepatitis B and Hepatitis C. Subjects will be informed about this requirement in the consent form.

7.3 Special Safety Considerations

7.3.1 MRI-related Risk Minimization

Participants will be appropriately screened for metals as will all personnel who enter the room that contains the MRI scanner. This screening will involve a self-reported MRI safety assessment as per local site policy, and assessment with a ferromagnetic metal detector. All females will have a pregnancy test prior to each MRI scan to ensure that they are not pregnant before being scanned. The following are common sources of risk:

<u>MR sounds.</u>

The MR scanner produces tapping sounds during operation, which may reach very loud levels. To minimize any discomfort from this noise, the participant will be provided with disposable earplugs that suppress external noise levels but do not eliminate voice communication with the scanner operator. The participant will have earplugs, which allow for blockage of environmental noise while maintaining communication and audibility of stimuli. If the participant finds the noise from the scanner objectionable, he/she may stop the study at any time.

Claustrophobia. Some people feel claustrophobic in the MR scanner. If this happens the scan would be stopped immediately. Simulation with the mock scanner will be offered prior to actual scanning to familiarize participants, and minimize this risk.

Neurostimulation. In some cases it is possible that subjects might experience neurostimulation effects, such as muscle twitches and tingling sensations, due to the rapid switching of magnetic field gradients used in these examinations. There are no known risks associated with these effects. Stimulation of the muscles of the heart, causing an abnormal heart rhythm is much less likely to occur. The devices used in this research create magnetic field gradients within the limits specified by the FDA.

Change in Body Temperature. A slight increase in body temperature may occur in the presence of radio frequency waves. A significant, deleterious increase in temperature is very unlikely at the settings employed in this study, which are within FDA guidelines.

RF Antenna Effects. If metal wires or electrodes are attached to a person being imaged, radio frequency signals from the MR scanner may induce sufficient electrical currents in the wires to cause burns where the wires or electrodes contact the skin. If wires or electrodes are present, the scanner operator will inspect and arrange them to minimize the risk of induced currents.

Quench Hazard. The MR scanner uses liquid nitrogen and liquid helium. It is remotely possible that the liquid nitrogen and helium could boil off rapidly and fill the magnet room with extremely cold dense gaseous nitrogen and helium, which can be dangerous if breathed for more than a few moments. When the scanner operator notices a quench, immediate assistance will be provided to anyone inside the magnet room.

Pregnancy. Although there is no known risk to a pregnant woman or her fetus from a MRI scan, women of child-bearing age will be asked to take a urine pregnancy test. If they decline to take the test, they will not be eligible for participation. If the test is positive, they will not be able to participate. There were no adverse effects on embryo-fetal viability, intrauterine growth, or morphological development seen in pivotal reproductive toxicity studies conducted in rats and rabbits (see

Investigator's Brochure). Those who become pregnant during the study will be excluded, and will have appropriate medical care and follow-up arranged.

7.3.2 Data Protection

All subject information will be kept confidential, and only members of the investigative team with appropriate Protection of Human Subjects and HIPAA training will have access to the data. Data will be maintained and secured in locked file cabinets or password-protected electronic media stored on devices approved and maintained for this purpose by Yale University (data coordinating site) in compliance with relevant regulations. Each site will keep a copy of the neuroimaging, behavioral and physiological data at their site. At all sites, digital media and filing cabinets are located in locked offices. A numbering code will be used to assign a unique identifier to each subject. The identification key will be digitally stored separately from all other data, using an encrypted, password protected database. All of the information obtained from subjects is referred to by code number, and kept locked in confidential files. This information is only available to study investigators and to relevant regulatory authorities upon request. As per agreement with the National Institute of Mental Health (NIMH), de-identified data will be shared publicly on the NIMH Data Archive (NDA https://nda.nih.gov/).

7.3.3 Vulnerable subjects

Schizophrenia is a debilitating and burdensome psychiatric illness with prominent cognitive deficits, and no targeted treatments for cognitive deficits. This clinical trial would be a first towards understanding specific neural mechanisms that can be targeted to improve cognition in patients with schizophrenia.

7.3.4 Phlebotomy and IV placement

Bruising, infection and thrombosis can occur with placement of the intravenous line. Having these procedures performed by experienced personnel using good clinical technique minimizes these risks. An experienced physician or nursing staff, as done in our previously completed studies, will perform this aspect of the protocol. Blood volume collection: The total amount of blood donated as part of this study is approximately 70 ml based on approximately 27 ml obtained for baseline laboratory tests, and approximately 40 ml (4 ml per blood levels sample, two samples per test visits, and 5 test visits). For the optional blood draw for genetics, an additional approximately 20 ml of blood will be drawn.

For those patients receiving IV placement, normal saline will be infused at 20 mL/hour. This is considered a slow infusion rate and will be done in order to keep the IV open and avoid clotting.

7.3.5 Blood sampling for pharmacokinetics, preparation, and storage

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, pharmacokinetics samples obtained within approximately 15% of the nominal time (e.g., within 9 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document. Sites will be provided materials and training for collecting these samples. Following collection, all samples will be spun, aliquoted and stored at each site, and then sent in batch to a collaborating site, Columbia University, for further storage at -80º Celsius. All processing of samples will be done at Columbia University by the Irving Institute for Clinical and Translational Research. To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in a locked, limited-access facility. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record.

7.3.6 Minimizing risk associated with genetic testing.

Genetic samples will be identified with a code number; a password-protected computer file will link subject information to this code. Materials for collecting genetic samples will be provided to each site, and the collected samples will be sent to Yale University for storage. Samples will be stored in a locked -80° C freezer. Any samples shared with other investigators as part of future research protocols utilizing this repository will be identified only by code number; no personal identifying information will ever accompany these samples. Any extracted genetic data will then be made available through the National Institutes of Health database of Genotypes and Phenotypes (daGaP).

7.3.7 Minimizing risk associated with confidentiality.

Patient's charts and written research records will be stored in a locked file cabinet in a secure office, accessible only to the principal investigator and other study personnel. Electronic records of clinical and research data will be stored on a password-protected personal computer. Participants will complete electronic questionnaires in the lab that are on REDCap, which is HIPAA compliant. REDCap is password protected, and will enable de-identified completion of all online questionnaires. We have obtained a Certificate of Confidentiality from the National Institutes of Health to provide maximum protection for the confidentiality of

subjects' clinical and research data.

7.3.8 Minimizing risks associated with neuropsychiatric testing and evaluation.

Some of the questions in the psychiatric interviews may be uncomfortable for the subject to answer. Potential participants may refuse to answer any specific questions or discontinue the interview at any time. The tasks and structured interviews may be tiring, but every effort will be made to avoid making subjects tired. Breaks will be offered frequently and subjects can quit at any time. During the evaluation, unanticipated psychiatric and medical information may be uncovered. In that case, findings will be discussed with the subject and appropriate follow-up will be advised.

7.3.9 Benefits to the participant.

As detailed in the consent form, there may be some benefit as a result of study participation, but no guarantee that individual benefit will be gained from participation in this study.

7.3.10 Alternatives to participation.

Participants are welcome to withdraw at any time, and to refuse participation in the study. The only alternative is to not participate in this study. Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.

8. SCHEDULE OF ASSESSMENTS

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Visit Windows		*Up to 8 weeks from last visit*	*Between 48 hours-2 weeks of last visit*	*Between 48 hours-2 weeks of last visit*	*Between 48 hours-2 weeks of last visit*	*Between 48 hours-2 weeks of last visit*	*Up to 1 week from last visit*
Informed Consent	**X**						
Baseline bloodwork (CBC, CMP, Hepatitis B and C, HIV, optional genetics) EKG, health history, physical exam	**X**						
SCID-V	**X**						
Fagerstrom Test for Nicotine Dependence	**X**						
Calgary Depression Scale for	**X**						

Schizophrenia							
Beck Anxiety Inventory	**X**						
Columbia-Suicide Severity Rating Scale, baseline	**X**						
PRA	**X**						
Edinburgh Handedness Inventory	**X**						
Penn CNB n-back letter task only	**X**						
Spatial Working Memory task (training)	**X**						
Flashing Checkerboard task (practice)	**X**						
Randomization for dose of CVL-562	**X**						
Mock scanner experience (optional)	**X**						
COVID-19 testing	**X**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**
MRI Safety Assessment	**X**	**X**	**X**	**X**	**X**	**X**	
Urine toxicology	**X**	**X**	**X**	**X**	**X**	**X**	
Urine pregnancy test	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**	
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	**X**	
PANNS, pre-dose	**X**	**X**	**X**	**X**	**X**	**X**	
Spatial Working memory task and Flashing Checkerboard Task (refresher**)**		**X**	**X**	**X**	**X**	**X**	
Dose of CVL-562		**X**	**X**	**X**	**X**	**X**	
Lifestyle Questionnaire, pre -dose		**X**	**X**	**X**	**X**	**X**	
Neuroimaging session, including structural MRIs, Spatial Working Memory Task--fMRI,		**X**	**X**	**X**	**X**	**X**	

resting-state fMRI, ASL, flashing checkerboard stimuli, and DWI (for first visit only), post-dose							
Blood draw for CVL-562 levels, post-dose (pre-scan and post-scan)		**X**	**X**	**X**	**X**	**X**	
Columbia-Suicide Severity Rating Scale, since last visit; pre-dose and post-dose		**X**	**X**	**X**	**X**	**X**	
PANNS, post-dose		**X**	**X**	**X**	**X**	**X**	
PennCNB battery, post-dose		**X**	**X**	**X**	**X**	**X**	
Adverse events	X	**X**	**X**	**X**	**X**	**X**	**X**
Follow-up/Debriefing							**X**
Final labwork (CBC, CMP)							**X**

Table 4. Schedule of Assessments. Visit 2 will occur 8 weeks after consent. All participants will be called approximately 24 hours after each treatment visit (Visits 2-6) to assess for adverse effects. All participants will be called 1 month after the final visit (Visit 7) to assess for lingering adverse effects. For those participants that need to be re-screened, all screening measures will be repeated except the SCID-V, the PRA and the Edinburgh Handedness Inventory.

9. ASSESSING AND REPORTING ADVERSE EVENTS

9.1 Definition

Adverse Event. An adverse event (AE) is defined as any untoward medical occurrence in a study participant taking the study drug(s) which does not necessarily have a causal relationship with the study drug(s). An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug(s) or protocol-specified procedure, whether or not considered related to the study drug(s) or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or severity) of a pre-existing condition that is temporally associated with the use of the study drug(s), is also an adverse event.

Serious adverse event. A serious adverse event (SAE) is an AE that fulfills one or more of the following criteria:
1. Results in death
2. Is immediately life-threatening
3. Requires in-patient hospitalization or prolongation of existing hospitalization

4. Results in persistent or significant disability or incapacity
5. Results in a congenital abnormality or birth defect
6. Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

9.2 Evaluating Adverse Events Including Serious Adverse Events

AE Severity
An investigator who is a qualified physician will evaluate all adverse events for severity according to the following criteria:

- Mild (Grade 1) corresponds to an event not resulting in disability or incapacity and which resolves without intervention
- Moderate (Grade 2) corresponds to an event not resulting in disability or incapacity but which requires intervention
- Severe (Grade 3) corresponds to an event resulting in temporary disability or incapacity and which requires intervention
- Life-threatening (Grade 4) corresponds to an event in which the study participant was at risk of death at the time of the event
- Fatal (Grade 5) corresponds to an event that results in the death of the study participant

AE Expectedness
An investigator who is a qualified physician will evaluate AEs for expectedness. AEs can be 'Unexpected' or 'Expected'. Most common Expected AEs include headaches, nausea, fatigue and vomiting. Please refer to the investigative brochure (IB) for additional information.

Unexpected AEs are those AEs in which the nature, severity, or frequency is not consistent with either:

1) The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as the IRB-approved research protocol, any applicable investigator's brochure, and the current IRB-approved informed consent document, or (b) other relevant sources of information, such as product labeling and package inserts; or

2) The expected natural progression of any underlying disease, disorder, or condition of the study participant(s) experiencing the AE and the study participant's predisposing risk factor profile for the AE.

AE Attribution
An investigator who is a qualified physician will evaluate AEs for attribution. The investigator must attempt to determine if an AE is in some way related to the use

of the study drug and define an attribution category. This relationship should be described as follows:

· Definite – The AE is clearly related to the study drug.
The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug. The AE improves upon discontinuation of the study drug and reappears upon repeat exposure.

· Probable – The AE is likely related to the study drug.
The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition OR the event cannot be the effect of a concomitant medication.

· Possible – The AE may be related to the study drug.
The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug OR the event could be the effect of a concomitant medication.

· Unlikely – The AE is doubtfully related to the study drug.
AE does not have temporal relationship to intervention, could readily have been produced by the study participant's clinical state, could have been due to environmental or other interventions, does not follow known pattern of response to intervention, does not reappear or worsen with reintroduction of intervention.

· Unrelated – The AE is clearly NOT related to the study drug.
The event is clearly due to causes distinct from the use of the study drug, such as a documented preexisting condition, the effect of a concomitant medication, or a new condition, which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unrelated to the use of the study.

All SAEs will be reported to the project manager within 24 hours of the site becoming aware of the event.

9.3 Procedures

- AEs will be recorded from the time the consent form is signed through 30 days after the last visit (i.e., at the one month follow-up from Visit 7). In addition, SAEs will be reported to the appropriate regulatory authorities, the IRB of Record, and investigators in accordance with all applicable laws and regulations.

- AE reporting must also be carried out by each participating site investigator, according to their local policies and procedures, to the IRB responsible for oversight of their subjects. A copy of the IRB's acknowledgement will be forwarded to the study project manager. In addition, all AEs will be recorded on an Adverse Event Log at each site and entered in REDCap within 72 hours of the site staff becoming aware of the event. All AEs must be followed until resolution or stabilization.

- Unanticipated and unexpected problems involving risk to the subject and/or others, whether related or unrelated to participation in the study, must be reported within 24 hours of the site staff becoming aware of the event to the study project manager. The project manager shall report all SAEs to the Sponsor Principal Investigator, who shall review and evaluate the evidence, and collaborate with the site PI on the final determination regarding attribution for reporting purposes to the following: FDA, Data Safety Monitoring Board (DSMB), Advarra, and/ or Cerevel.

- SAEs which occur any time after the study participant has consented until one month (defined as 30 days) after Visit 7 (i.e., at the final follow-up phone call) which are unexpected and possibly, probably, or definitely related to the research must be reported by the participating site to the study project manager within 24 hours of the site staff becoming aware of the event.

- FDA and Cerevel Reporting
- The Sponsor Principal Investigator's Investigational New Drug (IND) office will report SAEs to the FDA (if required) via an IND Safety Report on 3500A MedWatch form according to FDA 21CFR312.32 within 15 calendar days of the event occurring (within 7 days if the event is fatal or life-threatening). The Sponsor Principal Investigator's project manager will also report to Cerevel within that same time period.

- Advarra Reporting
- Each site investigator and/or designee will promptly report unanticipated problems occurring at the site to Advarra as per their written policies and procedures. SAEs that do not require prompt reporting will be reported at the time of continuing IRB review per their written policies and procedures via the Advarra CIRBI platform.

- Reporting to DSMB and NIMH
- Any actions taken by one entity in response to adverse event reports will be reported to the other entities. SAEs that are unexpected, and possibly, probably, or definitely related to the intervention will be reported to the DSMB by the study project manager in writing within 24 hours of awareness of the event. All other SAEs, expected or non-serious adverse events, will be reported to the DSMB in the DSMB data reports submitted every 6 months or at the time of continuing IRB review of the study, and to the FDA in the IND annual report. DSMB recommendations/outcomes will be made available to the NIMH.

- COVID-19-related AEs and SAEs
- All AEs and SAEs that are confirmed, or suspected to be related to, COVID-19 will be tracked within the REDCap system. These AEs and SAEs will be evaluated and reported using the same criteria as other AEs and SAEs.

9.4 Criteria for stopping study

For individual subjects, the stopping criteria are:
- Withdrawal of consent and/or patient decision;
- Loss to follow up;
- Changes to eligibility based on inclusion/exclusion criteria;
- Clinical judgment of the investigator or at request of subject, sponsor, or regulatory authority;

Criteria for Stopping or Suspending Enrollment:
-
- Assessment that risks outweigh benefits in the view of either the DSMB, the study investigators or study sponsors
- Decision by sponsors to withdraw funding or cease pursuing completion of the study.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design and Power

10.1.1 Primary Endpoint

To test if CVL-562 has dose-related effects in schizophrenia patients on neural biomarkers of D1R/D5R stimulation. The proposed research includes 120 female and male adults (18-45 years) who meet diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder and who are presenting early in their psychosis course (i.e., <5 years of psychosis duration since first frank psychotic episode). We will make every attempt to balance our recruitment

efforts with regard to sex.

All preprocessing of imaging data will follow Human Connectome Project (HCP) pipelines(67). For each CIFTI-based gray-ordinate, least-squares coefficients will be generated independently reflecting BOLD signal during task conditions. We will use a general linear model to fit the hemodynamic response function (HRF) using a finite impulse response function (FIR) for the timepoints covering the encoding (timepoints 1-2) and delay epochs (timepoints 3-14) and the natural decay in the HRF (timepoints 15-20). Assessing the HRF across these 20 timepoints for each task condition (motor, spatial working memory, distraction-near and distraction-far) will allow us to examine the effects of dose response across our epochs of interest. From these general linear models, we will form within-subject contrasts for second-level analyses. We will use non-parametric combination (NPC) to examine the multivariate effects of dose (5 levels) and task condition (motor, spatial working memory, distraction-near and distraction-far) at each timepoint within each voxel of an independently defined mask of spatial working memory regions from the prior work of Dr. Cho (co-investigator). When compared with an ANOVA or related MANOVA, NPC provides a more statistically efficient and robust approach for this primary endpoint, while still allowing for testing of dose-dependent effects of drug on the task BOLD signal at different timepoints(68). NPC has the additional advantage of accommodating the multivariate and potentially non-normally distributed nature of our endpoints. Furthermore, NPC maintains better power at fixed sample sizes than traditional multivariate tests, which have increasing power as the number of modalities increases, until an inflection point, after which traditional test power declines. Significant voxels will be determined using non-parametric statistics and corrections for multiple comparisons as appropriate.

As this is a multi-site neuroimaging project, we will validate neuroimaging data acquisition, transfer and processing prior to clinical data collection. These will be tested using members of the research team who will undergo neuroimaging procedures at each site. Scanning the same persons at each site will allow the research team to compare the image acquisition, as well as the collection of behavioral and eye-tracking data, at each site. We have opted for this instead of the exclusive use of phantoms, as task-based images would not be possible to collect with phantoms. Furthermore, we have opted to use research personnel who travel to each site, rather than examining the first few patients recruited, as we would like to examine image acquisition within-subject, and fully compare sites. Use of our recruited patients would not allow for within-subject comparisons of sites as the clinical protocol is meant to be carried out at one site. Ongoing stability of MRI scanners will be checked using regular phantom scanning.

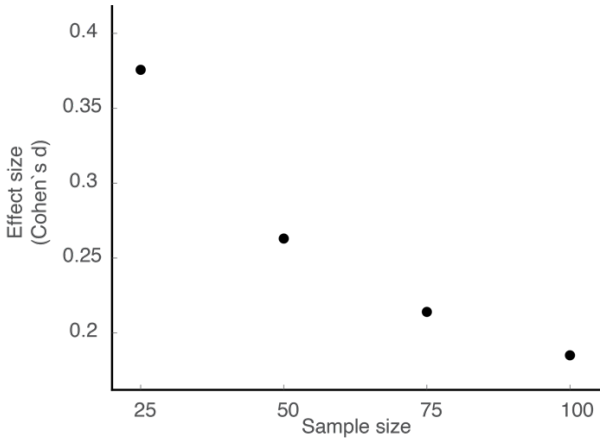

Figure 2. Power Calculation for the Primary Endpoint.

Power: The Primary Endpoint is concerned with within-subject repeated measurement of the CVL-562 dose response on the neuroimaging index. Therefore, the key power consideration is for a group-level within-subject t-test for the combined partial t-tests (Cohen's d). With anticipated attrition we anticipate a final sample of N=100 complete patient datasets across all sites. However, given that data quality and retention may lead to smaller eventual samples, we projected detectable effect sizes using a projected power of at least 80%, and $p<0.05$. Given our study design, and the NPC approach, we will be able to detect small-to-medium effect sizes (0.18-0.37) for sample sizes ranging between 25-100 participants with full data. Here, we provide an illustration of the achieved effect sizes at 80% power across possible sample size ranges (Figure 2).

10.1.2 Secondary Endpoint 1

The dose-response-based change in BOLD signal will be examined for each individual participant to see how many participants exhibit a change in BOLD signal. For each individual, a binary outcome will be calculated based on the dose x timepoint x task condition within subject analysis of BOLD signal. We will report the proportion of participants that exhibits a dose response and assess whether this is related to baseline working memory performance.

10.1.3 Secondary Endpoint 2

We will test if CVL-562 produces a dose-related modulation of sWM performance. We will leverage behavioral data generated during neuroimaging to quantify dose-related CVL-562 effects on sWM performance and also on sWM performance with distraction. Here, the outcome measure will be the sWM performance measured as the angular difference between the target presentation and the participant's response. We will conduct a 4 (task condition--motor, spatial working memory, near-distraction, far-distraction) x 5 (dose) repeated measures ANOVA. Post-hoc analyses will be conducted to demonstrate the directional effects of behavioral performance with respect to dosing. All statistics will be corrected for multiple

comparisons.

10.1.4 Secondary Endpoint 3

We will directly examine the association between sWM performance and task-evoked BOLD signal. An analysis of variance of the dose-dependent effects of CVL-562 on the task-evoked BOLD signal will be conducted as described for the Primary Endpoint, but instead will use the trial-by-trial regressor of sWM performance as a covariate. sWM performance will be measured as described in Secondary Endpoint 2, and will be treated as a covariate of interest in the above-specified general linear model. An effect of a 5 (drug dose) x 4 (task condition) interaction with the sWM precision covariate would indicate that the drug has an effect of BOLD signal change that is specifically associated with a change in trial-by-trial sWM performance.

10.1.5 Secondary Endpoint 4

We will conduct an analysis of variance of the dose-dependent effects of CVL-562 on the functional connectivity of brain regions during spatial working memory. In contrast to the task-evoked modeling, here we will use 'time point' selection methods to isolate specific time points during the delay period of each trial, which we will combine into a time series. This BOLD signal will be used to co-vary a given region of interest with the rest of the brain. Given prior work by our team we will focus on the fronto-parietal control network (FPCN) as a 'seed' region for this task-evoked FC analysis. Specifically, we will quantify covariation of the extracted FPCN signals with all other CIFTI greyordinates. This index of FPCN 'functional integrity' will be obtained across sWM conditions and CVL-562 doses for each subject and will then be entered into 2nd-level random effect analyses.

10.1.6 Secondary Endpoint 5

We will conduct an analysis of variance of the dose-dependent effects of CVL-562 on the resting state functional connectivity using a data-driven global brain connectivity (GBC) metric. Notably, GBC examines connectivity from a given voxel (or area) to all other voxels (or areas) simultaneously by computing average connectivity strength—thereby producing an unbiased approach as to the location of dysconnectivity. Also, unlike typical seed approaches, GBC involves one statistical test per voxel (or area) rather than one test per voxel-to-voxel pairing, substantially reducing multiple comparisons. Per-subject GBC will be obtained for each CIFTI greyordinate at each CVL-562 dose for each subject and will then be entered into 2nd-level random effect analyses.

10.1.7 Secondary Endpoint 6

Resulting resting state GBC maps will be compared against transcriptomic maps of genes relevant to psychotic disease processes from the Allen Human Brain

Atlas (https://human.brain-map.org/) using correlation analyses. This will allow us to see whether spatial patterns of resting state GBC map onto regions enriched for gene expression relevant to schizophrenia and related illnesses.

10.1.8 Exploratory Endpoint 1

We will conduct exploratory analyses to test whether genetic variants are related to BOLD signal changes in response to CVL-562. Genetic variants examined may include, but are not limited to, those genes involved in CVL-562 metabolism, the dopamine 1 receptor, or schizophrenia illness development.

11. ADMINISTRATIVE AND REGULATORY

11.1 Multicenter Management and Coordination

The Yale University Coordinating Site Project Management team will support the PI with the multi-site management aspects of this trial. This includes, but is not limited to, study start-up, regulatory assistance (IRB submissions, amendments, and renewals), provision of template study forms (tracking and eligibility checklists, etc.), site qualification and activation, training, and overall project management. The Coordinating Site Project Management team will provide tools to assist the study teams in conducting the trial appropriately and according to ICH Good Clinical Practice.

The Coordinating Site Project Management team will ensure that all participating sites undergo training in which all key study personnel will be instructed study procedures, informed consent, source documentation requirements, safety and adverse event reporting, Good Clinical Practice guidelines and additional study related topics. This training will be conducted by the Yale Center for Clinical Investigation (YCCI) Study Monitor and/or Project Management staff and documentation of completion will be required for all personnel. The PI will be available to site investigators for questions and re-training (if necessary).

After a site initiation visit, which includes Good Clinical Practice (GCP), participating sites will receive a regulatory start up packet from the Project Manager or designee prior to beginning study procedures. The start up packet will contain all required regulatory documentation and procedures that will need to be completed prior to site activation. Upon satisfaction of these requirements, each site will receive a site initiation letter from the Project Manager or designee indicating the site is fully activated and can begin enrollment and study procedures. All regulatory documents will be maintained on site and accessible for monitoring visits.

11.2 Data safety and monitoring plan (DSMP)

11.2.1 Safety Evaluations

Review of safety data will be conducted on all participants who have signed informed consent. Any safety concern or new information that might affect either the safety or the ethical conduct of this trial will be immediately forwarded to the principal investigator. Any adverse events that occur during the study will be recorded on the adverse event case report form in the eCRFs in REDCap The site investigators will be responsible for informing the IRB per local policy.

11.2.2 Safety Monitoring

The principal investigators, in conjunction with Yale Center for Clinical Investigation (YCCI), will provide primary oversight data and safety monitoring. They will be responsible for reviewing and monitoring compliance and deviations of this study. The sponsor Principal Investigator, the Institutional Review Board (IRB), the FDA or the NIMH have the authority to stop or suspend the study or require modifications.

The principal investigators will review the data from this protocol bi-annually, at a minimum. Information to be reviewed includes: a summary report generated from the study database (which includes participant accrual, adverse events (including SAEs), and deviations), as well as monitoring reports. Other information and/or data will be provided upon request. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO) that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The Principal Investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings or via email as they are reviewed by the principal investigator. The protocol's research monitor(s), study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of unanticipated, serious adverse events within 5 days of the event becoming known to the principal investigator.

11.2.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will meet approximately annually (prior to first randomization, end of first year of randomization, and completion of last subject). Study progress summaries would be provided to the DSMB members

approximately three weeks prior to each meeting. The DSMB is entrusted to review serious adverse events (SAE)s within 7 days, review adverse events (AEs) on an annual basis, and to monitor recruitment progress in order to evaluate study feasibility. Recruitment reports would be provided to the DSMB every 6 months with an optional face-to-face meeting at that time.

11.2.4 Study Site Monitoring

The principal investigators and YCCI are responsible for monitoring the performance of all of participating sites. This will be performed by conducting a study site initiation visit, as well as regularly scheduled monitoring visits and/or remote monitoring throughout the life of the protocol. Should travel be deemed difficult due to the COVID-19 pandemic or other related reasons, monitoring, including the study site initiation visit, may be remotely conducted. At the end of the trial, the monitor will then perform a study site close-out visit at all participating sites.

YCCI will utilize their standard initiation, monitoring and close-out visit reports. Following each site visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be sent to each investigative site.

During monitoring visits, some of the items that will be reviewed are the following:

- Training of the sites
- Site personnel qualifications to participate in the trial
- That study related documents are current
- That regulatory compliance is accomplished
- That each subject has signed the informed consent
- That the current and approved protocol is complied with (including reporting and logging of all protocol deviations)
- That all SAEs and AEs have been reported appropriately
- That source documentation matches CRFs

YCCI will document the required study monitoring activities in a detailed Clinical Monitoring Plan.

11.3 Confidentiality & Security of Data

11.3.1 Data Security and Storage

Each site will collect data using HIPAA trained personnel, and all electronic source data and neuroimaging data will be centrally stored at Yale University or at the University of Pennsylvania (for relevant questionnaires). Each site will keep a copy of the neuroimaging, behavioral and physiological data they have collected. Any data with paper sources will be stored at the site that collected the data. Electronic data will be stored and analyzed as de-identified, and the only

database where identifying information can be linked to a de-identifier will be encrypted and password protected. This database will only be accessible by specific study personnel. All study personnel will receive HIPAA compliance training. All paper data and personal health information will be de-identified and kept in lockable cabinets and lockable offices. As per requirements from the National Institute of Mental Health (NIHMH), de-identified data will be shared and made publicly available on the NIMH Data Archive (NDA, https://nda.nih.gov/).

11.3.2 Informatics Equipment and Tools

XNAT and REDCap resources will be used for data-sharing, data storage and transfer. The clinical and neuroimaging data-sharing and organization will use a 2-prong neuro-informatics strategy deployed at Yale: i) Clinical behavioral data will be stored and shared via the REDCap database; ii) The de-identified neuroimaging data and other multi-modal data sources will be stored and shared via the Extensible Neuroimaging Archive Toolkit (XNAT), which readily integrates with REDCap. REDCap is a free, secure, web-based application designed to support data capture for research studies (http://project-redcap.org). The system was developed by a multi-institutional consortium initiated at Vanderbilt University. The PI's team at Yale will use a fully HIPAA-compliant REDCap database, which is optimized for capture of longitudinal assessments. Importantly, the REDCap database is fully compatible with the XNAT system, which is an informatics platform for managing, exploring, and sharing neuroimaging data (http://www.xnat.org), developed at Washington University in St. Louis. Specifically, XNAT is designed to facilitate quality control procedures and provides secure access to and storage of both clinical and neuroimaging data. XNAT follows a 3-tier architecture that includes a data archive, user interface, and middleware engine. Data can be entered into the archive as XML or through data entry forms. Newly added data are stored in a virtual quarantine until an authorized user has validated it. XNAT subsequently maintains a history profile to track all changes made to the managed data. User access to the archive is provided by a secure web application. The web application provides a number of quality control and productivity features, including data entry forms, data-type-specific searches, searches that combine across data types, detailed reports, and listings of experimental data, upload/download tools, access to standard laboratory workflows, and administration and security tools. The research team will upload de-identified DICOM and/or NIFTI images. These images will be maintained via the XNAT database on the Yale servers and storage systems. As noted, the clinical information captured in REDCap can be readily integrated into XNAT for joint analyses. Furthermore, the XNAT database is deployed as part of the Human Connectome Project, providing a well-tested and robust long-term strategy for data management and pipeline workflow as proposed here.

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