Title of Study: A Double-Blind Trial of Adjunctive Valacyclovir to Improve Cognition in Early Phase Schizophrenia

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1.0 Introduction

Schizophrenia is a serious mental illness whose etiology is unknown. Cognitive impairments are a prominent feature of the illness and contribute to the social disability that is common in individuals with the disorder.[1] Currently there are no established treatments for the cognitive impairments associated with the disorder. A previous pilot study found that early course individuals with schizophrenia who were seropositive for the Herpes Simplex Virus 1 (HSV-1) and received adjunctive valacyclovir showed improvement in performance on some cognitive tasks compared to those who received adjunctive placebo.[2] Schizophrenia subjects who were HSV-1 seronegative were excluded from the trial. The current study is undertaken to confirm and extend these findings and determine if HSV-1 seropositive status confers cognitive enhancing effects of valacyclovir.

We intend to test the hypothesis that cognitive functioning in early course schizophrenia will be improved by treatment with the antiviral drug, valacyclovir, in subjects who are seropositive for HSV-1. We will enroll 70 adult subjects who are HSV-1 positive and 105 who are HSV-1 negative across US study sites; subjects will be individuals early in the course of schizophrenia. Subjects will be randomized to receive adjunctive valacyclovir, 1.5 g twice per day, or placebo over the 16 weeks of the trial. All subjects will continue to seek regular medical care and adhere to a regimen of psychiatric medications prescribed by their treating psychiatrist.

2.0 Scientific Background and Rationale

Cognitive Impairments in Schizophrenia

As a group, individuals with schizophrenia perform more poorly than age-matched controls on measures of verbal memory, executive functioning, attention, and processing speed.[3,4] Along with the characteristic positive and negative symptoms of schizophrenia, these cognitive impairments are a central feature of the disease and do not remit when psychotic symptoms subside. Cognitive impairments have been identified as a major contributing factor to the social disability associated with the disorder and its high burden of disease.[5] Given the importance of cognitive impairments in schizophrenia, a number of interventions, both pharmacologic and psychosocial, have been developed for their remediation.[6,7] However, to date, none has been established as clearly effective and implemented in routine clinical care.

The etiology of cognitive impairments in schizophrenia is not known. However, recent studies (reviewed by Prasad et al., 2012) show an association between exposure to Herpes viruses, particularly Herpes Simplex Virus Type 1 (HSV-1), and the severity of cognitive impairment in schizophrenia. Herpes viruses are enveloped, double stranded DNA viruses that are capable of infecting humans and many other animal species. HSV-1 can infect the central nervous system of otherwise healthy individuals and establish latency resulting in a lifelong infection.[8] In a previous study of 229 outpatients with schizophrenia, Dickerson et al. found that serological evidence of HSV-1 was an independent predictor of cognitive dysfunction; much of the difference in cognitive functioning between HSV-1 seropositive and seronegative groups could be attributed to immediate memory performance.[9] An association between seropositivity to HSV-1 and cognitive deficits was also found in three other independent schizophrenia samples[10-12] and further supported by neuroimaging data.[10,13] Evidence further suggests that brain related

impairments associated with HSV-1 exposure appear to worsen with time in early course HSV-1 exposed individuals with schizophrenia.[14]

Valacyclovir

Valacyclovir is the oral L-valyl ester prodrug of acyclovir and is converted to acyclovir via first-pass hepatic metabolism. Valacyclovir's properties have been reviewed.[15,16] Valacyclovir is approved by the United States Food and Drug Administration (FDA) for the treatment of herpes zoster and genital herpes and for the suppression of herpes virus infections including HSV-1.[17] Acyclovir is phosphorylated by viral thymidine kinases to its active form. This form inhibits DNA synthesis through competitive inhibition of viral DNA polymerase. Maximum plasma concentration of acyclovir is achieved in 1-3 hours after oral administration and the elimination half-life is 2.5-3.6 hours. Acyclovir is predominantly eliminated by glomerular filtration and tubular secretion. Valacyclovir is widely prescribed and considered to be relatively safe and well tolerated.[17]

Risks and Discomforts Associated with valacyclovir:

In clinical trials in adult patients, adverse events commonly observed more frequently with valacyclovir than placebo and at a rate of ≥10% are:

- Headache
- Nausea
- Stomach pain

In clinical trials in adult patients, adverse events observed more frequently with valacyclovir than placebo and occurring at a rate of <10% but >1% are:

- Dizziness
- Painful periods (females only)
- Joint pain
- Depression
- Vomiting
- Fatigue (sleepiness)
- Rash
- Low blood cell counts (neutrophil and platelet)
- Inflammation of the nose and throat
- Upper respiratory tract infection
- Increased liver enzyme levels (signs of liver damage)

The following are rare but are considered serious adverse reactions:

- **Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS):** This is a blood clotting problem which can be fatal. Cases of TTP/HUS, in some cases resulting in death, have been reported in patients who have advanced HIV disease and in patients who have had transplants and are on valacyclovir
- **Acute Renal Failure (kidney failure):** cases have been reported in elderly patients, those with underlying kidney disease, patients taking other drugs that may cause damage to the kidneys, and patients without adequate hydration (dehydrated)
- **Central Nervous System Effects:** agitation, hallucinations, confusion, delirium, seizures, and encephalopathy (brain swelling) have been reported in adult patients who received higher-than-recommended doses of valacyclovir[17]

The recommended dosage for suppression of recurrent genital herpes is 500-1000 mg taken once daily. Safety and efficacy of this regimen have been established for patients receiving these doses for up to 1 year. In a large-scale, 1 year, dose finding study for valacyclovir use in genital herpes suppression, 5.1% of all patients enrolled had discontinued their therapy because of an adverse event.[18] The percentages for discontinuing therapy were similarly distributed among the 6 treatment groups of the study (4 valacyclovir groups at 250 mg, 500 mg, 1 g once daily, or 250

mg twice daily; 1 acyclovir group at 400 mg twice daily; and 1 placebo group).[18] Valacyclovir adverse events reported in this study include headache, rhinitis, infection, flu-like syndrome, pharyngitis, nausea, back pain, diarrhea, abdominal pain, sinusitis, and dyspepsia. The frequency of these adverse events to valacyclovir was similar to that observed in patients receiving placebo. Abnormal laboratory tests for anemia, leukopenia, thrombocytopenia, AST (SGOT), and serum creatinine were also evaluated and the frequency of adverse events to valacyclovir was similar to that observed in patients given placebo and no association was observed between valacyclovir treatment and any abnormal laboratory test.[18] Doses up to 8 grams per day were used in pre marketing studies.[17] The study medication dose for this study will be 1.5 g by mouth, twice daily. This dose is identical to the University of Pittsburgh pilot trial (see below) and it is adequate for suppressive HSV-1 therapy.[17] We are proposing to use the dose of 1.5 g twice daily because this was the dose shown to be effective in the Prasad study.

Pilot trial of valacyclovir augmentation in early course schizophrenia

In a recent pilot study at the University of Pittsburgh, Prasad et al randomized 24 HSV-1 seropositive individuals with schizophrenia who were within 10 years of illness onset to receive valacyclovir 1 g orally twice daily for 2 weeks followed by 1.5 g orally twice daily for 16 weeks vs. identical appearing placebo.[2] All patients were maintained on prescribed antipsychotic medication throughout the course of the trial. At the end of the trial, subjects in the valacyclovir group showed significantly greater improvement in - working memory and visual memory than did subjects receiving adjunctive placebo. There were no significant differences between groups in psychotic symptom severity or in other cognitive domains. The medication was well tolerated by study subjects and the dropout rates were similar between the valacyclovir and the placebo group. Because there was not a HSV-1 seronegative comparison group, it could not be determined if the seropositivity of the cohort was the key factor that contributed to the positive cognitive results.

3.0 Specific Aims

The Primary Aim of the Study is:

1. To determine the efficacy of adjunctive valacyclovir, in comparison to placebo, to improve visual (Brief Visuospatial Memory Test) and working (composite score of the Spatial Span and Letter Number Span tests) memory in individuals who are HSV-1 positive and early in the course of schizophrenia. We hypothesize that individuals who are HSV-1 positive, but not those who are HSV-1 negative, will demonstrate significant valacyclovir efficacy for visual and working memory.

The Secondary Aims of the Study are:

1. To evaluate the efficacy of adjunctive valacyclovir, in comparison to placebo, to improve general cognitive performance as measured by the MATRICS composite score in HSV-1 positive and negative subjects.
2. To evaluate the efficacy of adjunctive valacyclovir, in comparison to placebo, to improve functional performance and quality of life as measured by the USCD Performance-Based Skills Assessment, Version B (UPSA-B), Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) and Personal and Social Performance Scale (PSP) and to improve global functional assessments as measured Clinical Global

Impressions Severity Scale (CGI-S) and Clinical Global Impressions Severity Improvement scale (CGI-I) scores in HSV-1 positive and negative subjects.

3. To evaluate the efficacy of adjunctive valacyclovir, in comparison to placebo, for general and positive symptoms as measured by the PANSS total and Marder subscale factor scores and negative symptoms as measured by the NSA-16 in HSV-1 positive and negative subjects.
4. To evaluate the tolerability and safety of valacyclovir treatment in this population.
5. To explore changes in the levels of inflammatory markers - HSV2, CMV, EBV, CRP, and Toxoplasmosis – and their relationship to treatment outcomes.

4.0 Study Design

One hundred and seventy-five subjects (N=70 HSV-1 seropositive and N=105 HSV-1 seronegative) will be randomized 1:1 to receive adjunctive valacyclovir or adjunctive placebo for a 16 week period. The primary outcome that will be assessed is improvement in changes in visual and working memory scores in HSV-1 positive and negative subjects over the course of the study. We will also measure the overall cognitive functioning and the severity of psychiatric symptoms over the course of the study and will evaluate the tolerability and safety of valacyclovir treatment in this population. In addition, we will explore the relationship between changes in the levels of inflammatory markers (HSV2, CMV, EBV, CRP, and Toxoplasmosis) and treatment response over the course of the study.

5.0 Study Population (Inclusion/Exclusion Criteria)

Inclusion Criteria

1. 18 to 40 years of age at study entry.
2. Able to give written informed consent.
3. DSM IV-TR Diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder as confirmed by Structured Clinical Interview for DSM-IV-TR (SCID)
4. Onset of schizophreniform disorder, schizophrenia, or schizoaffective disorder within the past eight years as defined by first medical records documentation of these conditions
5. Outpatient or inpatient.
6. Clinical stability as defined by:
    a. CGI-S score of less than or equal to 4 (moderately ill) at randomization AND
    b. Subjects must not have experienced an exacerbation of their illness within 4 weeks prior to randomization leading to an intensification of psychiatric care in the opinion of the investigator. Examples of intensification of care include, but are not limited to: inpatient hospitalization, day/partial hospitalization, outpatient crisis management, or psychiatric treatment in an emergency room AND
    c. Antipsychotic treatment stability for at least 4 weeks prior to randomization (no change in antipsychotic dosing, addition of any new antipsychotic medication, or discontinuing an antipsychotic medication)
7. Fluent in English.

8. Female subjects of childbearing potential must test negative for pregnancy at screening visit and agree to use a single, effective, medically acceptable method of birth control for the duration of the study.

Exclusion Criteria

1. Known IQ less than 70 as determined by medical history.
2. IV drug use within previous three month prior to study entry.
3. Any serious active medical condition that affects brain or cognitive functioning (e.g., epilepsy, serious head injury, brain tumor or other neurological disorder) in the investigator's opinion.
4. Known medical history of Human Immunodeficiency Virus (HIV)
5. Receipt of valacyclovir or chemically-related medication within 2 weeks prior to randomization.
6. History of hypersensitivity to valacyclovir or acyclovir as determined by self-report and medical history.
7. DSM-IV diagnosis of substance dependence within 3 months of study entry (with the exception of nicotine or caffeine dependence).
8. Subjects who have participated in a clinical trial with any pharmacological treatment intervention for which they received study-related medication in the 4 weeks prior to screening AND subjects currently receiving treatment (within 1 dosing interval plus 4 weeks) with an investigational depot formulation of an antipsychotic medication.
9. Females who are pregnant or planning to become pregnant or breastfeeding or planning to do so during the study period.
10. Subjects with current acute, serious, or unstable medical conditions, including, but not limited to: inadequately controlled diabetes, asthma, COPD, recent cerebrovascular accidents, acute systemic infection or immunologic disease, unstable cardiovascular disorders, malnutrition, or hepatic or renal disease, renal including renal failure, gastroenterologic, respiratory, endocrinologic, neurologic, hematologic including thrombotic thrombocytopenia purpura/hemolytic uremic syndrome, or infectious diseases
11. Subjects who require concomitant treatment with any other medication other than those allowed as specified in Attachment 2, or with any other medication specifically excluded in Attachment 2.
12. Clinically significant electrocardiogram (ECG) abnormality prior to randomization as defined by: subjects with a corrected QT interval (Bazett's; QTcB) >450 msec (male) or >470 msec (female) prior to randomization. Repeat ECGs will be conducted at the discretion of the principal investigator or medical designee.
13. Test positive for (1) Hepatitis C virus antibody, (2) Hepatitis B surface antigen (HBsAg) with or without positive Hepatitis B core total antibody.
14. Subjects with moderate to severe renal impairment as defined by creatinine clearance (CrCl) < 60 ml/min (measured by the Cockcroft-Gault equation) at screening.
15. Subjects with hepatic impairment as defined by liver transaminases or total bilirubin > 3 × upper limit of normal (ULN).
16. Subjects considered a high risk for suicidal acts – active suicidal ideation as determined by clinical interview OR any suicide attempt in 90 days prior to screening.
17. Subjects who demonstrate overtly aggressive behavior or who are deemed to pose a homicidal risk in the investigator's opinion.
18. Subjects currently receiving cognitive remediation therapy at time of study entry

19. Subjects who have had electroconvulsive therapy (ECT) within 12 months of study entry or who will have ECT at any time during the study.

6.0 Subject Recruitment

Subjects will be recruited through referring community mental health centers, treatment providers (including day treatment centers and inpatient units), and self-referrals through advertisement and word-of-mouth. Additionally, subjects will be invited to participate if they are included in previously established site registries.

7.0 Study Procedures

See Study Procedures Table Attachment 1.

8.0 Clinical Assessments and Procedures

The following assessments will be administered at one or more visits during the duration of the study according to the Study Procedures Table (Attachment 1). All assessments will be completed by study personnel based on interviews with the subject or based on questionnaires completed by the subject.

Diagnostic Interview
The Structured Clinical Interview for DSM-IV-TR (SCID-I/P Patient Edition) will be used to confirm the diagnosis of a psychotic disorder and/or rule out other diagnoses. The SCID-IP is a semi-structured interview designed to evaluate DSM-IV-TR Axis I diagnoses.[19] An abbreviated version of the SCID may be used at the discretion of the principal investigator. Inclusion diagnosis criteria will be verified.

Clinical Global Impressions Severity Scale (CGI-S)
The CGI-S will be used for repeated evaluations of global psychopathology. The CGI-S scale is widely used in schizophrenia research and is a single 7-point Likert scale rating severity of psychopathology on a scale of 1 (normal, not ill) to 7 (very severely ill).[20]

Clinical Global Impressions Severity Improvement Scale (CGI-I)
The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point Likert scale, ranging from very much improved (1) to very much worse (7).[20]

The Positive and Negative Syndrome Scale (PANSS)
The PANSS will be the primary assessment instrument for psychopathology. The PANSS contains 30 items that assess symptoms of psychotic disorders including positive, negative and general psychopathology. The PANSS was chosen because of its widespread use in clinical studies of psychosis, and its demonstrated reliability in assessing psychopathology across diverse patient populations.[21]

MATRICS Consensus Cognitive Battery (MCCB)

The MCCB will be administered according to Attachment 1. It is a reliable cognitive battery (test-retest reliability ~0.7 for most tests. Small but statistically significant practice effects have been noted with speed of processing and problem-solving subtests (1/5th of standard deviation). To overcome these practice effects, alternate forms of MCCB will be implemented in this study. The total average administration time of MCCB is approximately 75 minutes. MCCB is comprised of seven cognitive domains and 10 related tests (Trail Making Test: Part A; Brief Assessment in Cognition in Schizophrenia: Symbol Coding; Hopkins Verbal Learning Test-Revised; Wechsler Memory Scale-Third Ed: Spatial Span; Letter-Number Sequencing; Neuropsychological Assessment Battery: Mazes; Brief Visuospatial Memory Test-Revised; Category Fluency: Animal Naming; Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions; and Continuous Performance Test-Identical Pairs. For each cognitive test, a multi-item score will be derived based on the raw item values according to the MCCB scoring manual. Each of the individual item raw scores is standardized to age- and gender-corrected t-scores (mean=50, standard deviation=10). Each test will be converted in to a domain score, with Working Memory and Speed of Processing domains consisting of 2 and 3 tests, respectively. The visual and working components of the MCCB will be administered first because they represent the primary aims of the study.[22]

UCSD Performance-Based Skills Assessment-B (UPSA-B)

The UPSA-B is a performance-based assessment of improvement in functional capacity. Participants are asked to role-play tasks in 2 areas of functioning: communication and finances. The communication subtest revolves around a series of 9 role-play exercises using an unplugged telephone. The finance subtest tests the patient's ability to count change, read a utility bill, and write checks. Scores are assigned for each of the 2 subscales and a provided formula is used to calculate an UPSA-B Total Score (range = 0-100).[23]

Personal and Social Performance Scale (PSP)

The PSP scale is a 100-point, single item, clinician rated scale to assess 4 domains of functioning, including personal and social relationships, socially useful activities, self-care and disturbing and aggressive behaviors.[24]

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

The Q-LES-Q-SF), a 16-item scale based on subject report of life satisfaction and to assess deficit symptoms.[25]

Negative Symptom Assessment Scale – 16-item (NSA-16), a primary outcome measure, is used to help clinicians rate behaviors (not psychopathology) commonly associated with negative symptoms of schizophrenia. The scale rates subjects on 16"anchors," is a semi-structured, clinical interview, and each item is rated from 1 to 6. The total score is the sum of the 16 specific items and ranges from 16 to 96; a higher score indicates greater severity of illness. In addition, there is a global rating which represents the overall assessment of a subject's negative symptoms. The rating should not be an average of any particular behavior, but a gestalt of everything observed in the interview.[26]

Habits

Use of alcohol, tobacco, and recreational drugs since last assessment will be collected at each visit.

Heath Resource Utilization
Resource utilization data (outpatient community based medical and psychiatric visits) will be collected for comparative purposes.

9.0 Safety Assessments and Procedures

The investigator is responsible for appropriate medical care of subjects during the study. The investigator remains responsible for the following, through an appropriate health care option, adverse events that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Vital Signs: Vital signs will be assessed at study visits per Study Procedures Table (Attachment 1). Vital signs include: body weight, height (Visit 1 only), blood pressure, heart rate, waist circumference (optional per study site), and temperature (optional per study site). Blood pressure and heart rate will be taken in a seated position or supine position after a rest period of five minutes.

Medical History: The subject's lifetime medical history will be taken during the screening period. Medical history includes previous and current diseases.

Physical Examination: A physical examination including a neurological examination and an assessment for active infections, including orolabial lesions.

Electrocardiograph (ECG): A supine, 12 lead ECG will be performed according to the Study Procedures Table (Attachment 1). Potentially clinically significant ECG abnormalities will be interpreted by a local cardiologist at the discretion of the investigator and/or medical designee.

Suicidality: Suicide-related events will be assessed and evaluated at every visit through a clinical interview by a trained clinician designated by the site PI.

*Any abnormal findings and severity, causality or sequelae will be documented. Clinically significant changes in vital sign measurements, ECGs, labs, or findings during physical examination (including orolabial lesions) and findings during the clinical interview from baseline will be documented as adverse events and causality will be assessed.

10.0 Criteria for Repeat Assessments, Rescreening, and Discontinuation

Repeat Assessments
Screening assessments can be repeated within the screening window under the same screening number with the exception of eligibility criteria related rating scales/questionnaires. Subject diagnosis confirmation will not be repeated.

Rescreening
Subjects who screen fail may be rescreened one time, under a new screening number. If a subject is rescreened, all screening assessments (with the exception of the diagnosis confirmation) must be repeated and the stability criteria timelines must be met.

Discontinuation
Subjects will be discontinued under the following circumstances:

1. Study Medication Non-Compliance: Significant noncompliance is defined as missing seven or more consecutive days of study medication or more than 24 cumulative days of study medication during the entire study.
2. Subjects who have the following lab values while on study medication:
    - Liver transaminase levels >3 times the ULN
    - Hemoglobin <9
    - White blood cells <1500
    - Serum creatinine >1.5
3. Subjects who develop moderate or severe renal impairment as defined by CrCl <50 ml/min (measured by the Cockcroft-Gault equation) while on study medication
4. Female subjects who become pregnant while on study medication
5. Subjects who require more than 50% increase in their dose of antipsychotic medication OR the addition of a new antipsychotic medication will be reviewed by the principal investigator and discontinuation will be addressed on a case-by-case basis as clinically indicated.
6. Subjects who require treatment with any excluded concomitant medications (See Attachment 2)

If a subject discontinues from the study, discontinuation assessments will be at the discretion of the investigator.

A subject may withdraw from the study medication at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons.

11.0 Laboratory Assessments

Study associated laboratory assessments (blood and urine) will be collected at time points specified in Study Procedures Table (Attachment 1) and analyzed by a local laboratory with the exception of the urine dipstick assessments which will be collected and analyzed onsite

A total of 36 mL of blood will be collected for screening assessments (Visit 1), 30 mL of blood will be collected at Visits , 6, and 10.

Laboratory assessments to be completed:

1. complete blood count with differential (CBC w/diff)
2. comprehensive metabolic panel (CMP)
3. uric acid level
4. creatinine clearance
5. calcium
6. lipid panel
7. hemoglobin A1c (HgbA1c)
8. thyroid stimulating hormone level (TSH)
9. pregnancy test (urine)
10. urine toxicology screen
11. urinalysis
12. hepatitis panel
13. serological assessment of antibodies to HSV1
14. inflammatory markers (HSV1, HSV2, EBV, HHV6, CMV, CRP, VZV, and Toxoplasmosis)

*All clinically significant abnormal laboratory findings subsequent to randomization will be repeated at appropriate intervals to establish resolution or until appropriate clinical follow-up can be established.

Serological Assessment of Antibodies to HSV1:

A serological assessment of antibodies to HSV1 will be completed by a central laboratory, Mayo Clinic Mayo Medical Laboratories, and results will be reported during the screening period prior to randomization for each subject. Results will be sent electronically to Indiana University Department of BioStatistics who will release the result to identified unblinded study personnel at each study site. The unblinded study personnel will be responsible for randomizing subjects to study treatment according to the stratified randomization block.

Inflammatory Markers

Inflammatory markers (HSV1, HSV2, EBV, HHV6, CMV, CRP, VZV, and Toxoplasmosis) will be assessed with methods previously described.[27] These serologic assessments will be performed centrally in Dr. Robert Yolken's laboratory at the Johns Hopkins University School of Medicine. These blood samples will be de-identified at sites prior to sending for analysis. Study site investigators will remain blinded to the results of these assessments until after the trial has been completed.

Optional Repository Participation

An additional 4ml of whole blood will be collected (2ml serum) and sent to Robert Yolken, MD at Johns Hopkins University School of Medicine repository from all consented subjects in the main study (collected at screening) for later unspecified inflammatory marker analyses related to psychiatric disorders. Subjects may refuse to participate in the repository without consequence to their participation in the main study. These samples will be given a unique subject number linking the main study subject number to the repository subject number at the site level. Samples will be sent to the Johns Hopkins University School of Medicine repository using the repository subject

number only. Non-identifying demographic information will be submitted to Johns Hopkins University School of Medicine repository at the time of sample submission. The code linking subject to repository subject number will be destroyed by sites at the end of the main study, truly de-identifying the samples. Subjects will be able to request sample destruction from the Johns Hopkins University School of Medicine repository by formal request to the main study site until the time the identifying code is destroyed at the site level.

12.0 Study Medication/Treatment

Valacyclovir hydrochloride and matching placebo capsules will be used as study medication for this study. Placebo capsules will look like valacyclovir capsules, with matching shape, taste, and color. Subjects will be instructed to take 6 capsules of study medication daily.

The investigator or his/her designee is responsible for explaining the correct use of the study medication to the subjects, verifying subject understanding and agreement, maintaining accurate records of dispensing and collection, and destroying all unused medication according to their pharmacy standard operating procedures at the end of the study. Subjects will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study medication so that the situation can be assessed.

Method of Assignment to Treatment
Subjects who meet all criteria for enrollment will be 1:1 randomized in a double-blind fashion to adjunctive treatment with valacyclovir or placebo at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence provided to sites by an unblinded biostatistics team at Indiana University. To minimize potential imbalance among treatment groups of factors that may influence efficacy outcomes, a stratified random assignment of subjects to therapy will be used to insure equal representation of HSV1 positive and negative subjects in the placebo and valacyclovir arms. The stratification factors used for this study include the investigative site.

Compounding and Pharmacy Oversight
Study medications will be sent to study sites at regular intervals from the University of Iowa which is contracted by Indiana University for preparation and shipping study medication for this study.

Study medication will be purchased directly through Indiana University. University of Iowa pharmacy will over-encapsulate the valacyclovir and create matching placebo capsules. Study medication will be stored according to the details on the product label (59 º to77º F).

Dosing
The dosing used in this study is 3 capsules of either valacyclovir or /placebo by mouth twice per day, given without regard to meals. Each valacyclovir capsule will contain 500 mg of active ingredient for a total daily dose of 3 grams per day. Dose reductions of 2 capsules per day will be permitted to address adverse events at the discretion of the site investigator.

Dispensing
Dispensing method will be chosen by each site and will include one of the following options:

Option 1: Bulk Supply/Local Pharmacy
Each investigative site will identify their local pharmacy used for dispensation to subjects. Indiana University will provide randomization numbers to each site. The local pharmacy will be responsible for randomizing subjects to groups and dispensing medication to subjects according to their local standard operating procedures. Each investigative site will remain blinded, but each site's pharmacy will hold their subjects treatment assignment which may be broken in the case of an emergency.

Option 2: Individual Blinded Packages/Unblinded Site Personnel
University of Iowa will label and package medication into individual packages for subject assignment by unblinded site personnel. Indiana University will provide randomization numbers to each site. Each investigative site will identify their unblinded site personnel to be used for package assignment to subjects. The unblinded site personnel will be responsible for randomizing subjects to groups and dispensing medication to subjects according to their local standard operating procedures. Each investigative site will remain blinded, but the unblinded site personnel will hold their subjects treatment assignment which may be broken in the case of an emergency.

Compliance
Compliance will be assessed at each visit by direct questioning and medication count of unused medication and packaging to be returned at each visit. Adequate study medication dispensing records will be obtained.

13.0 Concomitant Medication

The list of excluded medications and procedures is provided in Attachment 2.

Benzodiazepine Equivalents Use
The use of benzodiazepines/hypnotics/anxiolytics is permitted during the study (all study periods). Benzodiazepines should not be administered 8 hours before psychiatric evaluations during all study periods. Every effort should be made to use the smallest amount possible. Benzodiazepines should only be taken "as needed" (PRN), and not as a standing dose unless the subject has been receiving a stable dose of a benzodiazepine/hypnotic/ anxiolytic for at least 30 days immediately prior to Visit 1. Benzodiazepine usage, however, must be recorded in mg with valid start and stop dates, and should not be recorded with a "PRN" frequency.

Table 1 lists the only allowed benzodiazepine equivalents to be prescribed in this study. Subjects should not exceed the maximum daily dose of any individual agent as specified in Table 1.

The use of multiple benzodiazepines concurrently is discouraged.

Table 1. List of Benzodiazepine Equivalents

Benzodiazepine	Max Daily Dose
Lorazepam	6 mg
Temazepam	30 mg
Diazepam	30 mg
Flunitrazepam	6 mg
Phenazepam	2 mg
Clonazepam	1.5 mg
Nitrazepam	5 mg
Flurazepam	30 mg
Triazolam	0.25 mg
Oxazepam	60 mg
Chloral hydrate	2000 mg
Chlordiazepoxide	75 mg
Alprazolam	3 mg
Zolpidem	10 mg
Eszopiclone	3 mg

Anticholinergic Therapy

The use of anticholinergic medications is permitted during the study (all study periods) (Table 3). PRN anticholinergics should not be administered 8 hours before psychiatric evaluations during all study periods. Every effort should be made to use the smallest amount possible. Anticholinergic medications should only be taken "as needed" (PRN), and not as a standing dose unless the subject has been receiving a stable dose of the anticholinergic medication for at least 30 days immediately prior to randomization. In those cases the anticholinergic medication should be taken at the regularly scheduled time. Anticholinergic medication usage, however, must be recorded in mg with valid start and stop dates (and frequency if scheduled), and should not be recorded with a "PRN" frequency. If multiple anticholinergic medications are in use then use the equivalency table to determine maximum allowable daily dose (Table 4).

Table 3. Allowed Anticholinergic Medication

Anticholinergic	Maximum Daily Dose
Benztropine mesylate	6 mg
Biperiden	6 mg
Procyclidine	15 mg
Trihexyphenidyl (Benzhexol)	15 mg

Table 4. Estimated Anticholinergic Equivalency

Anticholinergic	Estimated Anticholinergic Equivalency
Benztropine	1 mg
Biperiden	1 mg
Diphenhydramine	67 mg
Procyclidine	2.5 mg
Trihexyphenidyl	2.5 mg

14.0 Adverse Events and Reporting

For the purposes of collecting and evaluating all information found during this clinical study, an **adverse event** is any undesirable or unexpected experience that occurs after informed consent has been obtained without regard to the possibility of a causal relationship, and without regard to treatment group assignment. All adverse events will be documented and all serious adverse events will be reported following local IRB requirements.

For non-serious adverse events, research staff will question each subject and will document the occurrence and nature of presenting condition(s). Pre-existing condition(s) and any change in the pre-existing condition(s) will be documented and/or the occurrence and nature of any adverse event.

A **serious adverse event** is any adverse drug experience occurring at any dose that: results in death, is life threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity, or results in congenital anomaly/birth defect.

All serious adverse events will be documented and reported to appropriate regulatory bodies.

15.0 Monitoring Randomization Assignments and Data Safety Monitoring Board

Throughout the course of the study, the study's senior statistician will evaluate unblinded randomization assignments to assess the equivalence of the two groups. If the randomized groups are not matched, the randomization procedures may be altered to ensure that the two groups do not differ on relevant variables.

Each investigative site will a have site specific **Data Safety Monitoring Board** (DSMB) which will be responsible for data and safety monitoring for each site. DSMB is responsible for reviewing study procedures, AEs, safety mailings (if applicable), enrollment, active subject progress, drop-out rates, and ongoing conduct of the research. The DSMB members can ask questions and make comments and/or recommendations to the investigators. The Institutional Review Boards (IRB) and SMC's are notified of significant findings by way of the DSMB meeting minutes at the time of continuing review according to each site's standard operating procedures. DSMB members must consist of physicians and scientists not listed as site investigators on this study. Data on the number of subjects enrolled and the number of AEs will

be reviewed by the DSMB at least bi-annually and more frequently if needed. The resulting report will be issued to the site specific IRBs and SMC at least at the time of IRB continuing review or more frequently by request. Any unanticipated events will be immediately directed to the lead investigators at each site who will follow their IRB reporting procedures.

16.0 Statistical Analysis

Power analysis

The effect sizes observed in the completed Prasad et al. 2012 study were used to estimate the sample size necessary for adequate power to detect differences in cognitive variables for the current study. The earlier study, which enrolled 12 patients in each group, saw changes in cognitive function with effect sizes that ranged from small (d=0.25) to quite large(d=1.21). An intent-to-treat (ITT) analysis will be adopted, which includes all randomized subjects. We will use two cognitive domains from the MATRICS battery, visual memory and working memory, as the primary outcome variables. Prasad reported effect sizes of Cohen's d=0.79 for working memory and d=0.97 for visual object learning when comparing valacyclovir to placebo in HSV-1-seropositive subjects. Forty percent of patients with schizophrenia are HSV-1 positive (Prasad et al in press; Dickerson et al 2003). A total of 175 subjects will be enrolled at 5 sites, with the expectation that 70 subjects will be HSV-1-seropostive and 105 subjects will be seronegative. With 70 HSV-1 positive subjects enrolled (35 per treatment group), we would be able to detect a minimum effect size of d=0.63 (a conservative estimate based on the Prasad study) for each of the two primary outcome measures at significance level alpha=0.05 using two-sided t tests. The Hochberg modification of the Bonferroni method to control Type 1 error will be used. With this method, the smallest of the p-values for the two outcomes is tested at p<alpha/2; if that test is rejected, the second outcome is tested at p<alpha We will achieve the same power when testing HSV-1 positive vs. negative subjects who are on valacyclovir using similar methods. We will test the treatment effects on the two primary efficacy measures (visual and working memory) with one-tailed tests at an overall alpha=0.1. Stratified randomization will be used to ensure the balance of HSV-1 status between the valacyclovir group and the placebo group.

Data Analysis

The primary objective of this study is to determine: 1) whether valacyclovir improves cognitive functioning in schizophrenia subjects who are HSV1 seropositive and early in the course of their illness, and 2) whether the improvement from valacyclovir differs in HSV1 seropositive and negative subjects. We hypothesize that subjects who received valacyclovir will show improvement in memory functioning, as measured by the visual and working memory domains of the MATRICS cognitive battery relative to their counterparts who received placebo, and the improvement exists in HSV-1 seropositive subjects compared to the seronegative subjects. All randomized subjects will be used using ITT analysis. This is the most conservative approach for detecting a treatment effect, because the inclusion of subjects who did not complete the intervention will serve to underestimate rather than overestimate any treatment effect. Sensitivity analyses including a subset analysis using completers only analysis will also be performed to test the robustness of the findings. Statistical tests will be performed based on one-sided test at the 10% level of significance with an adjustment for multiple comparisons for the 2 primary efficacy outcome measures with each primary measure tested at an alpha threshold of p<0.05 as noted above. One-tailed tests are planned because the main interest of this study is to

determine if valacyclovir is superior to placebo and thus has produced a sufficient efficacy signal in one or more of the two primary efficacy outcome measures to warrant further assessment in subsequent larger, confirmatory trials.

Baseline analysis will be conducted to summarize patients' characteristics in the two treatment groups for HSV-1 seropositive and seronegative subjects respectively. Demographics and relevant clinical variables, including symptom severity and antipsychotic dose equivalents, will be compared between treatment groups using two-sample t tests (for continuous variables) and chi-square tests (for categorical variables).

The primary outcome measures are the visual and working memory domains of the MATRICS battery. For each subject, a change score will be calculated for this domain, which quantifies the difference in cognitive performance from pre-treatment baseline to post randomization study visits. Unadjusted p-values from direct comparison of valacyclovir vs. placebo among HSV-1 positives, and HSV-1 positive vs. negative with active treatment will be reported using two-sample one-sided t tests.

The primary outcome measures (visual memory and working memory) and important secondary cognitive (MCCB composite score) and functional (UPSA-B, Q-LES-Q-SF) outcome measures will be assessed at baseline, visit 6 and visit 10. To analyze these measures, we will employ a mixed model for repeated measures ANCOVA, of the general form for each measure: Post-baseline score at visit i = baseline score + treatment + visit + HSV-1 status + interactions among treatment, visit, and HSV-1 status + other baseline covariates, where visit is a categorical measure denoting whether the post baseline score came from visit 6 or 10. Within-subject correlation will be modeled with an unstructured covariance matrix with 3 parameters (variances at visit 6 and 10, covariance between visits 6 and 10). In this model, the treatment effect estimates the average magnitude of the treatment differences at visits 6 and 10, and the treatment x visit interaction the difference in the magnitude of the treatment difference at visit 10 vs visit 6. Additional interactions involving treatment, HSV-1 and week estimate how the magnitude of treatment differences, on average or at visits 6 versus 10, is altered by HSV-1 status. No imputation will be needed to address missing data issue using the linear mixed model approach.

For PANSS scores, which are assessed at 4 post-baseline visits, we will also use mixed model ANCOVA with a similar set of fixed effects, but will compare the fit of linear or higher order polynomials to estimate time trends in treatment effects. In past studies in schizophrenia using the CGI, we have observed that 1) most values are clustered tightly among 3 or 4 of the 7 possible grades of severity, and 2) few subjects change more than 1 or 2 points. These features that suggest linear mixed models may be inappropriate for detecting change in the CGI. Accordingly, we will assess change in the CGI as follows: 1) For each subject, we will compute the Spearman rank correlation between visit number and CGI score for all visits observed, as a nonparametric measure of trend; and, 2) a Wilcoxon test will be used to compare the average magnitude of within-participant Spearman trend scores a) between all participants on Valacyclovir and Placebo; b) between participants on are HSV-1 seropositive and on valacyclovir or placebo; or, c) between participants on are HSV-1sero negative and on valacyclovir or placebo. We will use multiple imputation of missing CGI data to assess the sensitivity of these analyses to missing data.

Another analysis objective is to assess the safety and tolerability of valacyclovir treatment in this patient population. Safety data will be analyzed using incidence density analysis to compare the rates of adverse events (AEs) across groups. Incidence density analysis is ideal for adverse events comparisons, because event frequencies are adjusted for the total duration of follow-up, and thus corrects for different rates of follow-up between study groups. The occurrence of all adverse events will be compared, as will the occurrence of the following categories of adverse events: total AEs, serious AEs, psychiatric AEs, and AEs grouped by organ system. Survival analysis techniques will also be employed to compare retention time across groups. In addition, secondary analyses will include testing for drug versus placebo effects in all participants without consideration of HSV-1 sero status. All statistical analyses will be conducted using SAS 9.1.

17.0 Privacy/Confidentiality Issues

Confidentiality will be protected by ensuring all research staff have been properly trained in confidentiality and human subject research procedures, coding all subject information when possible, and by securing subject files in a locked filing cabinet or on secured databases with access available only to the investigator and research staff. Furthermore, data entered into a computer database will only use subject codes on secured computers that will be password protected with access available only to the investigator and research staff. Any screening information obtained from potential research subjects who subsequently do not participate in the research study will be destroyed.

18.0 Record Retention

Paper copies of medical records and source documentation will be kept for at least seven years after the study is closed with the IRB. One year after study closure, the documents may be shipped site specific long-term storage facility until destruction.

19.0 References

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ATTACHMENT 1

Study Procedures Table

	Screening Period Visit 1	Baseline Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Term-ination Visit 10
Day		0	14	28	42	56	70	84	98	112
Visit Window Intervals			12-16 days	12-16 days	12-16 days	12-16 days	12-16 days	12-16 days	12-16 days	12-16 days
(in days)	0-30 days	N/A	(+/- 2 days)	(+/- 2 days)	(+/- 2 days)	(+/- 2 days)	(+/- 2 days)	(+/- 2 days)	(+/- 2 days)	(+/- 2 days)
Informed Consent	X									
Demographics, Substance/ Medical/Psychiatric History, review of current and previous medications	X									
SCID	X									
Physical Exam	X									X
Health Resource Utilization		X				X				X
Habits[d]	X	X	X	X	X	X	X	X	X	X
ECG (triplicate 1 min apart)	X									
Vitals	X	X				X				X
Labs (CMP[b], CBC w/ diff)	X					X				X
TSH	X									X
Hepatitis Panel	X									
Uric Acid	X									X
Lipid Panel	X									X
HgbA1c	X									X
Creatinine Clearance	X					X				X
HSV1	X									
Urinalysis	X					X				X
Urine pregnancy test	X	X				X				X
Urine toxicology	X	X				X				X
Inflammatory markers	X									X
Repository[c]	X									
CGI-I			X	X	X	X	X	X	X	X
CGI-S and Suicidality clinical interview	X	X	X	X	X	X	X	X	X	X
PSP & Q-LES-Q-SF		X				X				X
MATRICS & UPSA-B		X				X				X
NSA-16		X		X		X		X		X
PANSS		X		X		X		X		X
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X
Medication Dispensation		X	X	X	X	X	X	X	X	
Medication Accountability			X	X	X	X	X	X	X	X

[a]Note: Visit 2 procedures may be split over 2 visits at the site discretion. Assessments should be no more than 7 days apart if split visit occurs.

[b]Note: Calcium level is included in the CMP panel.

[c]Optional. Consent must be obtained for participation in repository

[d]Baseline/Lifetime Habits is collected at the screening visit

ATTACHMENT 2

Concomitant Medication Table

Medication	Use approved in study
Alpha 2 agonists (eg., Clonidine)	Stable dose, no changes or additions
Aminoglycoside antibiotics (systemic)	No
Anticholinergics	Conditional [a]
Antidepressants	Stable dose, no changes or additions
Antiemetics (eg., metoclopromide, domperidone, other dopamine receptor blockers)	Stable dose, no changes or additions Conditional [b]
Antiepileptic mood stabilizers (Divalproex, Oxcarbazepine, Lamotrigine, or Carbamazepine) & Lithium	Stable dose, no changes or additions [g]
Antiepileptics, non-mood stabilizers	Stable dose, no changes or additions EXCEPT topiramate not allowed
Antifungals (systemic)	No
Antineoplastics	No
Antipsychotic medications	Conditional [c]
Antivirals (including trantadine)	No
Barbiturates	Conditional [b]
Benzodiazepines & related sedatives (eg. Zolpidem)	Conditional [a]
Bisphosphonates	No
Contraceptives	Stable regimen [g]
Creatine	No
Cyproheptadine	Conditional [b]
Decongestants (eg., pseudophedrine)	Conditional [e]
Dextromethorphan	Conditional [b]
Dicyclomine	No
Herbal medications or Over the Counter Medications w/ primary CNS activity	No EXCEPT fish oil is acceptable
H2-Blockers (cimetidine, probenecid, and ranitidine) [f]	No [f]
Interferons	No
Hydroxyzine	Conditional [b]
Immunoglobulins	No
Immunosupressants (DMARDs) (systemic)	No
Live attenuated vaccine	Caution [d]
Midrin	Conditional [b]
Minocycline	No
Muscle relaxants	Stable dose, no changes or additions Conditional [b]

(continues)

Concomitant Medication Table (continued)

Opiates/Opioids	Stable dose, no changes or additions Conditional [b]
Other Psychotropics Not Mentioned Elsewhere	Stable dose, no changes or additions
Penicillamine	No
Pentamidine	No
Roflumilast	Stable dose, no changes or additions
Tramadol	Stable dose, no changes or additions Conditional [b]
Trazodone	Stable dose, no changes or additions Conditional [b]
Vancomycin	No

[a]Conditional. See section 13.0 of protocol

[b]May be used PRN but should be avoided 8 hours prior to cognitive testing. Record time and date of last administration prior to assessments.

[c]Stable dose prior to study for four weeks prior to randomization with no more than 50% change in dose from baseline over course of study. May be used PRN but should be avoided 8 hours prior to assessments.

[d]Caution. Concomitant use of valacyclovir with live attenuated vaccinations can deminish the effectiveness of the vaccine. The CDC recommends stopping oral antiviral medication for 24 hours before the varicella zoster vaccine and for two weeks following vaccination.

[e]Conditional. Recommended for "as needed"/PRN use, no longer than 7 consecutive days and no administration 24 hours prior to cognitive testing. Participants may take an expectorant in lieu of a decongestant.

[f]Exclusionary H2 blockers include: cimetidine, probenecid, and ranitidine. Other H2 blockers are not explicitly exclusionary, but use caution when prescribed as all are renally excreted with a potential to interfere with renal excretion & increase acyclovir levels.

[g]For female patients on carbemazepine, oxcarbazepine, and lamotrigine, oral estrogen-containing contraceptives may not be effective (due to cytochrome p450 3A4 interactions).