Protocol Title:
Glutamate Reducing Interventions in Schizophrenia

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08/24/2020

Protocol Number:
7459

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Clinic:
Center of Prevention and Evaluation (COPE)

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Research Chief:
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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am proposing an amendment only to an existing protocol

Division & Personnel

Division

What Area Group does the PI belong to?
What Division/Department does the PI belong to?
Translational Imaging
Within the division/department, what Center or group are you affiliated with, if any?
COPE

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

na

Amendment

Describe the change(s) being made
We are submitting this amendment to revise this protocol to include that research staff will monitor each dose of POMA taken by participants via hipaa compliant video. We are doing this because an initial analysis of PK data indicated substantial nonadherence with POMA. We made this change to the PSF (Study Procedures, in bold, towards the end) and the CF (page 4, bolded). We are also changing the time of the PK blood draws from pre dose on days 7 and 14 to 2-3 hours after the dose on day 7 and right before the MRI on day 14 (Study Procedures, in bold, towards the end). We are making this change
because the half life of POMA is only a few hours and we think that peak rather than trough levels will be more informative. We have included clean and bolded versions of the patient CF.
Provide the rationale for the change(s)
Please see above.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
Please see above
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
Please see above. Yes, a change was made.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ MRI
✓ Use of Investigational Drug or Device
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research

✓ Adults who may have impaired decision-making ability
✓ Medically and Psychiatrically Healthy Subjects
✓ Adults

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIMH
Grant Name
Glutamate reducing interventions in schizophrenia
Grant Number
R61 MH112800-01
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
RFMH, Dr. Lieberman is the PI of the RFMH Subcontract

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Previous research suggests that elevations of a brain chemical called glutamate can lead to an increased risk for developing schizophrenia. If this research is correct, then medications that decrease glutamate may be able to prevent the development of schizophrenia. One medication that decreased brain glutamate is a medication called pomaglumetad (POMA). POMA has been tried several times in schizophrenia but without much success. We think that this may be because these people already had schizophrenia. In addition, the people who did these studies used doses of POMA that were too low and did not actually decrease glutamate. Third, the people who did these studies did not use a brain imaging method of measuring whether or not POMA affected glutamate levels in the brain.

To address these limitations of prior studies, we will administer several doses of POMA (low and high doses) over 14 days to individuals at clinical high risk for developing psychosis and use MRI brain imaging to determine whether these doses of POMA are affecting glutamate levels. In a second phase, we will use the dose of POMA that is found to decrease glutamate levels in a clinical trial in which we compare that dose of POMA with placebo in a standard clinical trial.

We will also perform a study to examine the stability of our MRI measures over up to 4 months in a healthy control population.

Background, Significance and Rationale

Background, Significance and Rationale
Studies suggest that abnormal elevations in extracellular glutamate can act as a pathogenic driver of schizophrenia, including in the hippocampus a brain region that neuroimaging studies suggest might be affected first and foremost. If this formulation is correct, then high glutamate should be considered a molecular target for drug discovery and agents that reduce extracellular glutamate should be an effective intervention. Pomaglumetad methionil (which we will call 'POMA') is one such agent, because as an agonist of presynaptic metabotropic glutamate 2/3 receptors this class of drug has been found to reduce glutamate release. Nevertheless, trials that have used POMA have to date shown little efficacy in patients with schizophrenia. Despite these failures, we believe that, based on the accumulative evidence, high glutamate is indeed a valid target and that two reasons might account for these initial failures. First, as these trials did not use a reliable brain biomarker of glutamate elevations there was no readout of 'target engagement', and thus it remains possible that these trials were false negatives. Second, and more importantly, schizophrenia is now thought to start in a prodromal phase before the onset of psychosis, and there is evidence to suggest that the prodromal stage might represent a unique time-window for therapeutic interventions, and so it possible that the drug was given at the wrong stage of the disease.

Pathophysiological support for these conclusions comes from our studies (Schobel et al, Neuron, 2013) in which we applied fMRI indicators of metabolism and volumetric MRI to patients in prodromal stages of the disease who then progressed to the psychotic stage, and to a mouse model of the disease. Collectively, these studies suggested that glutamate is a driver of hippocampal dysfunction, that fMRI measures are sensitive to glutamate elevations, and that glutamate-reducing drugs can ameliorate hippocampal

dysfunction. We also have completed preliminary studies using magnetic resonance spectroscopy, in which we show that hippocampal glutamate is elevated in prodromal stages of the disease.

Based on the results of these and other studies, we have recently proposed a mechanistic model of disease progression (Small, Neuron, 2014), which predicts that because of its distinct pathophysiological features the prodromal stage of disease is a unique time-window that is most amenable to glutamate-reducing interventions. This mechanistic model motivates this protocol in which we hypothesize that: 1) MRI based measures of hippocampal metabolism and glutamate can be used as in vivo biomarkers of target engagement when using a glutamate-reducing intervention. 2) Glutamate-reducing interventions will be most effective when administered to prodromal patients, and only when they are shown to engage their target. The R61 phase of this proposal is designed to test the first hypothesis, and the R33 phase is designed to the second. The current IRB describes the R61 phase.

We will also perform a study to examine the stability of our MRI measures over up to 4 months in a healthy control population.

Specific Aims and Hypotheses

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To perform a double-blind, randomized, phase Ib, multiple dose trial of 14 days of treatment with POMA (40mg bid, 80mg bid, 120mg bid, 160mg bid) in clinical high risk patients to determine which dose, if any, reduces hippocampal glutamate and metabolism using MRI techniques. The GO NO-GO decision will be whether or not any dose tested in the R61 phase of the trial decreases left CA1 CBV.

To examine the stability of our MRI measures over up to 4 months in a healthy control population.

Description of Subject Population

Sample #1

Specify subject population
Clinical High Risk
Number of completers required to accomplish study aims
12
Projected number of subjects who will be enrolled to obtain required number of completers
50
Age range of subject population
18-30

Sample #2

Specify subject population
Controls
Number of completers required to accomplish study aims
20
Projected number of subjects who will be enrolled to obtain required number of completers
30
Age range of subject population
18-30

Gender, Racial and Ethnic Breakdown
33% Caucasian, 33% African American, 10% Asian, 24% Mixed; 33% Hispanic; 70% male, 30% female
Description of subject population
As above

Recruitment Procedures

Describe settings where recruitment will occur

Patients will be told about the study by staff at the COPE clinic (IRB #6654R). If they are interested, they will then be referred to study investigators designated to obtain informed consent, who will describe the study in greater detail and then obtain informed consent. Specifically, patients interested in participation will be screened by study physicians and told about the study. They will be told about the procedures and risks, that the study involves randomization and the details will be explained. They will also be told that participation is voluntary, and of the extra study details beyond that of the COPE protocol itself and affiliated observational studies, including exposure to POMA and gadolinium contrast. If interested and eligible, patients will have an evaluation of their capacity to consent and invited to provide written informed consent.

Healthy control subjects will be recruited through #6654R as well as from other Area Psychosis research studies that include healthy control subjects who have expressed interest in additional research.

How and by whom will subjects be approached and/or recruited?
See above. All patients will be initially recruited through 6654R.
How will the study be advertised/publicized?
As above. Patients are initially recruited through 6654R.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number

NCT03321617

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Subjects may also be active in IRB #6654R, 7132R, 7342 (PI Girgis on them all) as they are longitudinal studies. However, no study procedures for the other studies will take place while active in the current study. Rather, the other studies are studies which involve an active period, followed by up to two years of longitudinal follow up before procedures are repeated (6654R is the screening/umbrella protocol for all COPE studies). Therefore, subjects will not actually be "active" in more than one study while part of the current study, and therefore subjects will finish this study before moving on to any other studies. Patients will be told about the study by staff at the COPE clinic (IRB #6654R). If interested, the study will be explained in greater detail by a study physician. **Healthy control subjects may also be recruited through 6654R or other Area Psychosis research studies though will only be active in one protocol at a time.**

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Clinical High Risk
Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. COPE Patient between the ages of 18-30 (Identified as at clinical high risk for psychosis as defined as a) attenuated psychotic symptoms; or b) brief intermittent psychotic symptoms c) schizotypal disorder or family history of psychotic disorder with recent decline in functioning (30 GAF points))	Structured Interview for Prodromal Syndromes/ Scale of Prodromal Symptoms (SIPS/SOPS)
2. Capacity to provide informed consent	Clinical assessment by research team and independent assessment of capacity
3. Currently using a reliable form of birth control (females **and males**)	Physician interview

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Metal implants in body or a history of metal working	Physician evaluation
2. Lifetime diagnosis of asthmatic symptoms within the past 3 years or known sensitivity to contrast agents	Physician evaluation
3. Lifetime diagnosis of renal failure/disease	Physician eval and laboratories
4. Acute neurological, neuroendocrine, or medical disorder including renal insufficiency (CrCl <60mL/min/1.73m2	Physician exam, electrolytes, CBC
5. Lifetime diagnosis of hypertension or diabetes or seizure disorder	Physician evaluation
6. IQ < 70	WTAR < 6
7. Acute risk for suicide and/or violence	Physician evaluation, suicidal or violent act in last 6 months, CSSRS
8. Pregnant, lactating	Urine pregnancy test
9. Current abuse of substances (alcohol, cocaine, stimulants, cannabis, opiates, sedative hypnotics)	SCID, utox
10. Current use or anticipated need for any antipsychotics or mood stabilizers (all antipsychotics, also Depakote, lithium, lamotrigine, pregabalin or any med with a mechanism of action like gabapentin) probenecid. **Patients may take selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors as long as they have been on a stable dose for at least 4 weeks before starting study drug.**	Physician Eval
11. More than one previous gadolinium scan	Physician Eval

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Controls

Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Healthy control between the ages of 18-30	Scid
2. Capacity to provide informed consent	Clinical assessment by research team
3. Currently using a reliable form of birth control (females)	physician interview

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Metal implants in body or a history of metal working	metal screener
2. Any neurological disorder	medical history
3. IQ < 70	WTAR < 6 (only if IQ < 70 is suspected)
4. Pregnant, lactating	urine pregnancy test
5. Current use of substances (cocaine, stimulants, cannabis, opioids, sedative hypnotics)	utox, SCID
6. Any history of use of a psychiatric medication	History
7. Any history of a DSM Axis I disorder with the exception of specific phobias and adjustment disorders	SCID

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
Yes
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6654R
Describe Study Consent Procedures
Patients will be told about the study by staff at the COPE clinic (IRB #6654R). If they are interested, they will then be referred to study investigators designated to obtain informed consent, who will describe the study in greater detail and then obtain informed consent. Specifically, patients interested in participation will be screened by study physicians and told about the study. They will be told about the procedures and risks, that the study involves randomization, and the details will be explained. They will also be told that participation is voluntary, and of the extra study details beyond that of the COPE protocol itself and affiliated observational studies, including exposure to POMA and gadolinium contrast. If interested and eligible, patients will have an evaluation of their capacity to consent and invited to provide written informed consent. We will explicitly ask all subjects if they are planning on having a gadolinium MRI scan within the 2 weeks before the study, during the study, or within 2 weeks after the study (we will place this in the consent form).

Control subjects will be similar told about the study and consented if they are interested. Controls will not require an independent assessment of capacity.

Remote/virtual Procedures: remote procedures will be similar to in person procedures except that we will use redcap to obtain signed consent (using the e signature feature) on the consent forms and hipaa forms. This may occur by either phone or video. If a subject is unable to use redcap for some reason, we will use a verbal consent procedure. When a verbal consent procedure is done by phone, CFs and HIPAA forms will be sent to participants, preferably in advance in possible, for their review and records (but not signed). We have requested a Waiver of Documentation of Consent in the Waiver section of the PSF. In these cases, a note-to-file will be added to the participant's chart on the date of the verbal consent procedure documenting the consent discussion and the participant's verbal consent, signed by the consenter.

We are confirming that the consent discussion process will include discussion of the technology HIPAA-compliant platforms to be used and any concerns the patient may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi.

We are also confirming that the consent discussion includes the of risks of possible loss of confidentiality with remote procedures, as well as the risk of attending the MRI or any other procedure in-person during the pandemic, and how these risks can be mitigated.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?
No
Is breach of confidentiality the main study risk?
No
Is consent for this research procedure ordinarily not required outside of the research context? Explain
For our remote/virtual consent procedures, we will use redcap. If a subject is unable to use redcap for some reason, we will use a verbal consent procedure. When a verbal consent procedure is done by phone, CFs and HIPAA forms will be sent to participants, preferably in advance in possible, for their review and records (but not signed). We have requested a Waiver of Documentation of Consent in the Waiver section of the PSF. In these cases, a note-to-file will be added to the participant's chart on the date of the verbal consent procedure documenting the consent discussion and the participant's verbal consent, signed by the consenter. We are requesting the waiver of documentation of consent because, in this case, we do not want subjects to send us PHI when it may not be sent in a private manner.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Girgis, Ragy, MD
Lieberman, Jeffrey, MD
Small, Scott
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
Yes
Methods/procedures for capacity assessment
Capacity will be assessed by a psychiatrist or psychologist licensed in NY state and who is not associated with this study **(patients only)**.

Study Procedures

Describe the procedures required for this study
a. COPE patients (IRB #6654R) Patients will be told about the study by staff at the COPE clinic (IRB #6654R). If interested, the study will be explained in greater detail by a study physician. Patients will provide written informed consent and capacity determined by a licensed, CITI trained MD or PhD psychologist at NYSPI.
b. Baseline measures (pre-randomization):
i. Serum laboratory tests (beta HCG if female, electrolytes, serum BUN/creatinine, CPK, urinalysis, liver function tests, CBC with differential, thyroid function tests); If eGFR <40 mL/min/1.73m2 or serum pregnancy test positive , then patients will discontinue the study (exclusion criterion for exposure to gadolinium.
ii.a urine toxicology screen
iii. general physical exam, including measures of weight, blood pressure, temperature pulse, respiration, EKG.
iv. 5cc of blood for DNA analysis
c. Structural Interview of Prodromal Syndromes (SIPS) to evaluate current prodromal symptoms at time of study entry
d. SCID to evaluate current psychiatric diagnoses including present of substance abuse
e. MATRICS, Hollingshead, GFS scales, GAF, CGI, SAFTEE, AIMS**,** CSSRS, Simpson Angus Scale
f. MRI with gadolinium contrast and MRS (one hour). All scans will be examined at the image console for gross structural abnormalities such as the presence of mass effects, hydrocephalus, and vascular malformations by study imager and study physician. Since the images obtained in this study are exclusively T-1 weighted, they will not be clinically read, except for screening for gross structural brain abnormalities by neuroradiologist within 7 days of the scan. Should there exist a gross structural brain abnormality, a neuroradiologist will immediately inform the principal investigator. The neuroradiologist will immediately provide an oral report followed by a handwritten or typed note to the PI and the Director of the MRI Unit. A final written transcript of the clinical reading will be provided
within two weeks of the oral report. The subject will be informed of the result, post-scan acquisition, by the study PI. Appropriate follow-up with the patient's primary care physician or appropriate sub-specialist and care setting will be immediately arranged for further diagnostic testing/treatment recommendations by study PI in consultation with the neuroradiologist.
Concomitant Medications: During the trial, no new concomitant psychotropic medications will be permitted of the following classes of medication: antipsychotic or mood-stabilizing medication. Antidepressant and antianxiety medication, if needed for clinical management, will be allowed, including lorazepam up to 1 mg daily (hypnotic, or for anxiety) if needed on a PRN basis. If a patient does require lorazepam, they will not take it for 24 hrs prior to MRI scan. If a study participant requires an excluded medication during the course

of the study, they will be discontinued from administration of the POMA, though complete all other study procedures. Other medications that do not interact adversely with POMA will not be changed during the study.

Treatment Design: Enrollment, randomization, blinding, and assessments for safety

Patients will be randomized in a double blind manner to 40mg bid, 80mg bid, 120mg bid, or 160mg bid of POMA. They will be randomized in a 1:1:1:1 ratio. The identity of medications will be blinded having every subject take an equal number of pills (e.g., someone taking 160mg bid will take 4 tablets of 40mg POMA bid, and someone taking 40mg bid will take 1 tab of 40mg POMA bid and 3 identical looking tablets of placebo bid). To minimize risk of nausea, we will taper medications up so that on day 1 subjects will take 40mg bid, on day 2 80mg bid (if at this dose or higher), on day 3 120mg bid (if at this dose or higher), and on day 4 160mg bid.

After subjects have completed their baseline procedures, they will be given a 7 day supply of POMA. They will return on Day 7 and have all baseline measures as described above, with the exception of the SCID and MRI. They will then be given another 7 days of POMA and return on day 14 when they will again receive all baseline measures including MRI with gadolinium injection, but not including the SCID and blood for DNA Analysis.

Medication adherence will be assessed by pill count.

Pregnancy Testing
As above, we will obtain a serum HCG at screening, as well as urine HCG before any MRI scan and on the day that study drug is dispensed if that does not occur on the same day as the first MRI scan.

Follow Up

We will perform a safety check in call 30 days after study participation. We may repeat the safety labs/EKG/physical as necessary after Day 14 if there is a clinical indication to do so.

PK Testing

We will obtain blood samples for PK testing of POMA on days 7 **2-3 hours after the dose and 14 right before the MRI scan.**

Phone Check Ins

Study physicians will perform phone check ins between days 1 and 7 and between days 8 and 14. **In addition, research staff will observe patients taking each of their doses via hipaa compliant video.**

Stand By

We will give all subjects the option of being a standby subject. Standby subjects will be asked to come in on a day when a brain scan is scheduled for another participant. If for some reason the original participant does

not complete the imaging procedures, the standby will be asked to participate in the imaging procedures in place of that person. If the original participant does complete the imaging procedures, they standby will be sent home. We expect that standbys will have to wait between 1-3 hours as a standby participant. Subjects can choose to be a standby subject by checking one of the boxes found at the end of the consent form. We may ask standbys to be standby subjects multiple times. In addition, we may schedule more than one standby for a given day.

We have attached a table that includes a summary of all procedures.

This trial will be monitored by a DSMB

Healthy Control Test Retest Study

Healthy control subjects will be screened with the SCID as well as a urine toxicology and urine pregnancy test. Eligible subjects will receive up to 4x1 hour MRI/MRS scans over a 4 month period. MRI scans will be done as described above, without gadolinium. Standby procedures will also apply to healthy control subjects.

Remote Procedures: Some of the visits may be conducted remotely using the telephone or HIPAA-compliant video teleconferencing. In particular, all procedures that can be done remotely including consent, capacity and clinical/behavioral assessments will be done remotely except for the blood draw and physical exam which will have to occur separate from MRI since these screening procedures are required before we begin the study (technically not required for MRI but we prefer to know if someone will be eligible for the study before we have people do MRI; we will submit individual exception requests if we want to perform an MRI without having received the results of labs and physical exam).

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:
• Infection Control/PPE – Guidelines
• Research participants will only come on-site if absolutely necessary for study procedures.
• No volunteers/externs on-site during Stage 1.
• Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
• COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Subjects will be discontinued from this study for any of the following reasons: a) relapse, defined as an increase of > 2 points on the CGI-S at any time point; b) the use of > 3 doses of p.r.n. clinically determined

benzodiazepines or any antipsychotics in a week; c) deemed to be clinically necessary in the opinion of the investigator based on laboratory information, physical examination, mental status examination, or any other clinical information; d) pregnancy; **e) seizure activity**. All attempts will be made to obtain end-of-study CBV scans and ratings for early discontinuations. The blind will be broken at the end of the study. Randomization/blind information will not be given to subjects.

Patients will be discontinued if they convert to psychosis. If this happens, standard treatment/referral procedures (as per #6654R) will be implemented. Namely, if they do not already have a clinician, they will be treated in COPE until an appropriate referral can be made.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
We will obtain up to 120 cc of blood at screening (safety labs **and blood for DNA**), day 7 (safety labs and POMA PK sample), and day 14 (safety labs and POMA PK sample) for a total of **50** cc over the course of the study (~3 tablespoons).

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

The Structured Clinical Interview for DSM-IV (SCID) (First e al., 2001) 45 min is a structured diagnostic interview done at baseline to evaluate potential exclusion criteria for the trial.

The Structured Interview for Prodromal Symptoms/ Scale of Prodromal Symptoms (SIPS/SOPS) 30 min (Miller et al.,1999) will be done at baseline, and on days 7 and 14. It includes the GAF.

The Global Functioning Scale: Role (GFS: Role; Niendam, Beraden, Johnson & Cannon, 2006), and The Global Functioning Scale: Social (GFS: Social; Auther, Smith & Cornblatt, 2006) 5 min.

Clinical Global Impression scale (CGI)-3 minutes measures overall clinical functioning.
Columbia Suicide Severity Rating Scale (CSSRS)-5 minutes assesses for suicidality.
MATRICS-60-90 minutes is a comprehensive measure of cognitive functioning.
Wechsler Test of Adult Reading (WTAR)-5 minutes is a measure of intelligence.
Simpson Angus Scale (SAS) 5 min measures extrapyramidal symptoms
SAFTEE 5 min is a measure of side effects

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Pomaglumetad
Manufacturer and other information
Lilly and Denovo
Approval Status
IND is approved
IND#
134867
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Lieberman, Jeffrey, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study

If subjects clinically require active treatment for new onset mood syndrome (major depressive or bipolar, anxiety symptoms, or psychosis during the study period or screening phase) patients will be immediately offered such treatment. Subjects will be ineligible for study participation if they meet any exclusion criteria as a result of such clinical developments. Since POMA is an experimental medication, it will not be available to subjects at the end of the trial.

Patients in this study will continue their usual treatment with their usual psychiatrist and clinician without interruption or changes. There is currently no standard best clinical practice (psychotherapeutic or psychopharmacologic) for prodromal stages of psychotic disease. Available antipsychotic therapies have been studied and are associated with improved prodromal symptoms and lessening of transition to psychosis, but are associated with a significant side-effect burden, including EPS, weight gain, and hyperlipidemia, amongst other side effects. The evidence for efficacy of cognitive-behavioral interventions for prevention of transition to psychosis is also mixed to date.

All COPE subjects receive up to 2 years of free, no cost treatment (medication management and therapy), though they would have to cover the cost of their medications.

Clinical Treatment Alternatives

Clinical treatment alternatives

If subjects clinically require active treatment for new onset mood syndrome (major depressive or bipolar, anxiety symptoms, or psychosis during the study period or screening phase) patients will be immediately offered such treatment. Subjects will be ineligible for study participation if they meet any exclusion criteria as a result of such clinical developments. Since POMA is an experimental medication, it will not be available to subjects at the end of the trial.

Patients in this study will continue their usual treatment with their usual psychiatrist and clinician without interruption or changes. There is currently no standard best clinical practice (psychotherapeutic or psychopharmacologic) for prodromal stages of psychotic disease. Available antipsychotic therapies have been studied and are associated with improved prodromal symptoms and lessening of transition to psychosis, but are associated with a significant side-effect burden, including EPS, weight gain, and hyperlipidemia, amongst other side effects. The evidence for efficacy of cognitive-behavioral interventions for prevention of transition to psychosis is also mixed to date.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

1) Risks and Discomforts Associated with LY2140023 (Pomaglumetd, “POMA”) Administration

Approximately 582 healthy subjects and 2877 subjects/patients with schizophrenia have been exposed to POMA in prior studies. Across groups, nausea, vomiting, increased heart rate, and eosinophilia as assessed by laboratory values were commonly reported (≥1% and <10%) in patients treated with POMA.

Healthy controls: 582 healthy control subjects received doses ranging from an acute dose of 5mg to 200 bid for up to 14 days. Most of the adverse events reported were mild, and the subjects recovered without sequelae. The most common AEs (≥10%) in clinical pharmacology studies conducted in healthy subjects were: nausea, headache, vomiting, and dizziness. The following SAEs have been reported in healthy subjects: infected sebaceous cyst (1), deep vein thrombosis (1), pulmonary embolism (2), and syncope due to vasovagal event (1). With the exception of syncope due to vasovagal event, none of these SAEs were reported by the investigator as related to administration of POMA.

Most pertinent to the proposed dose in this study, multiple doses of POMA, administered up to 160 mg BID, were well tolerated in the healthy subject population, including 5 healthy controls receiving 160 mg BID (greater or equal 320 mg per day) for 14 days and 2 receiving 200

mg bid without significant side effects. There were no serious adverse events and all subjects completed. The most commonly reported adverse events were headache, nausea, epistaxis, diarrhea, dizziness, somnolence, tremor, pruritus and feeling hot. The profile of drug-related adverse events were similar to those reported in previous clinical pharmacology studies in healthy volunteers, and those reported in clinical studies with patient populations. There were no dose limiting events observed in doses up to 160 mg BID. The study was terminated prematurely by the Sponsor in response to two cases of convulsions observed in an ongoing Phase 2 study in schizophrenia patients, involving dose levels lower than doses administered in this study. Although no serious adverse events occurred the healthy control dose escalation study, the decision was taken to stop the study whilst the 200 mg dose level was ongoing

There were generally no clinically significant values, changes, or trends in clinical laboratory data or vital signs. An increased esoinophil count was observed after 15 days of dosing with 40 mg POMA. However, similar eosinophil changes were not seen at higher dose levels, so there is no apparent dose dependency of the change. In addition, there were no concomitant cutaneous reactions associated with the eosinophil changes, so the clinical significance remains unclear. There were no clinically significant changes in ECGs which is consistent with findings, suggesting that doses of POMA up to 160 mg BID are not associated with QTc prolongation. This study incorporated EEG measurements to explore potential prodromal signs of convulsions at higher than previously administered doses of POMA. The results of the EEG measurements in this study showed that there was no abnormal EEG activity associated with POMA, administered up to 160 mg BID.

Patient populations: Table 6.4 from the IB (attached) provides a summary of TEAEs for patients who were assigned to take either placebo or POMA in completed studies. In the placebo-controlled studies, 727 patients were assigned to placebo, and 1555 were assigned to POMA . There was not a significant difference in adverse events when comparing patients taking placebo with patients taking POMA , 403 (55.4%) and 901 (57.9%), respectively. The common adverse events reported in ≥2% of patients treated with POMA were: schizophrenia (underlying disease-related events), eosinophilia, anxiety, acute extrapyramidal symptoms, vomiting, abdominal pain, insomnia, headache, nausea, anxiety, blood CPK increased, agitation, constipation, abdominal pain, and dyspepsia. Nausea was significantly higher in the POMA pooled group compared with the placebo group (6.8% vs. 4.1%, p=.005), as were vomiting (4.1% vs. 2.5%, p=.032) and eosinophilia (4.8% vs. 1.0%, p=.003).

The most common TEAEs reported in ≥2% of patients assigned to POMA in 1 or more of the completed long-term safety studies were: schizophrenia-related events, nausea, insomnia, headache, vomiting, nasopharyngitis, blood CPK increased, anxiety, decreased appetite, diarrhea, dizziness, tremor, fatigue, weight decreased, nasopharyngitis, upper respiratory tract infection, agitation, dyspepsia, bronchitis, back pain, cough, depression, restlessness, abdominal discomfort, blood pressure increased, constipation, rash, tooth ache, arthralgia, back pain, somnolence, akathisia, dry mouth, irritability, pruritus, and upper abdominal pain.

In the placebo-controlled studies there was a statistically higher incidence of abnormally high eosinophils at any time in the pooled POMA group compared with placebo (POMA 5.5%;

placebo 0.9%; p<.001). There was also a statistically significant mean increase in eosinophils during administration of POMA administration when compared to baseline or placebo.

The significance of the eosinophila is unknown but there have been no clear clinical correlates to the eosinophil elevations. There have been no other consistent or clinically significant changes in laboratory values in the placebo-controlled studies.

In other studies, people who took compounds similar to POMA have experienced rash, skin itching, or skin peeling. Because of these experiences, rash, itching of the skin or skin peeling will be closely monitored. Subjects will be asked at every visit about these skin conditions.

Most pertinent to the present project, 44 patients with schizophrenia completed a multiple dose escalation study over a dose range of 160 to 480 mg BID for 7 days. The tolerability of POMA dosing was improved after the first day of dosing. In general, the TEAEs of nausea and vomiting occurred more frequently on first exposure to POMA. There was no apparent trend in the severity of TEAEs with increasing dose. The MTD for was not reached in this multiple ascending dose study. There were no clinically meaningful changes in ECG parameters and no positive correlation between plasma concentrations of POMA and changes from baseline in QTc across all the doses. A dose of 400 mg, which was approximately 5 times the anticipated clinical dose, did not prolong QTcF to a clinically significant degree.

Deaths: There were 18 deaths reported in completed studies (out of over 3000 human exposures). In these 18 death cases, 12 patients were assigned to take POMA, 3 patients were assigned to take placebo, 1 patient was assigned to take olanzapine, and 2 patients did not take any study drug. Also, of these 18 death cases, 7 were completed suicides with 5 of those patients assigned to take POMA. Of the 12 patients assigned to take POMA, 5 of those deaths occurred after the study drug had been held or discontinued. Also, of the 12 patients assigned to take POMA, 9 of those deaths were considered to be not related to the study drug treatment by the investigator, while all 12 deaths were considered to be not related to the study drug treatment by the sponsor. A listing of death cases for completed studies is presented in Table 6.1 in the IB (attached).

SAE: Overall, there were 361 case reports of SAEs (excluding the 18 deaths in patients) in POMA clinical trials. In the placebo-controlled studies, 727 patients were assigned to placebo, and 1555 were assigned to POMA. There was not a significant difference in SAEs when comparing patients taking placebo with patients assigned to POMA, 25 (3.4%) and 43 (2.8%), respectively. The only SAE reported ≥1% patients was schizophrenia-related, with no statistically significant differences observed when comparing patients taking placebo with patients taking POMA.

Overdose: The effect of a single dose of activated charcoal on the PK of POMA and LY404039 was examined in healthy subjects. Activated charcoal reduced the area under the curve from time zero to infinity (AUC0-∞) and Cmax of both POMA and LY404039 by approximately 25% and 35%, respectively, when administered 1 hour after a single 80-mg dose of POMA . However, the median time to maximum concentration (tmax) of neither analyte was affected by administration of activated charcoal.

Signs and Symptoms: There is limited information on signs or symptoms of POMA overdose or on treatment of overdose in humans. In clinical trials, 1 case of ingesting approximately 1800 mg of POMA in combination with lorazepam was reported. The patient did not experience any significant medical consequences of the overdose and spontaneously recovered without medical intervention.

Management of Overdose: No specific antidote is known. Symptomatic treatment and monitoring of vital organ function according to clinical presentation is recommended.

Risk of Serotonin Syndrome

POMA increases levels of serotonergic metabolites in humans (Lowe et al., 2012) and therefore there is a theoretical increased risk of serotonin syndrome when POMA is administered with a serotonergic medication, such as an antidepressant. There is insufficient experience in humans to know whether this risk of more than theoretical. However, in order to protect against this risk, we will review serotonin syndrome as part of the standard consent process with all patients, include a full paragraph in risks section of the consent form discussing this theoretical risk, and review side effects at every visit, as previously described. In addition, we are already excluding individuals with any severe medical condition or history of seizure disorder, and have implemented a robust schedule for adverse event monitoring, including safety labs and medical/physical examination.

Seizure Risk

In all of the studies performed with POMA in human subjects, events of seizure were reported in 6 patients treated with POMA at 5, 20, and 80 mg BID. Additionally, seizures were reported in 1 patient randomized to risperidone and 1 patient during a placebo-lead in period. Seizures were reported in an additional 3 patients prior to them being randomized to study medication. There was 1 additional report of convulsion that was determined not to be seizures.

Specific Vulnerabilities

There are no known specific vulnerabilities for a CHR **(clinical high risk)** population. However, we will obtain an independent assessment of capacity for all subjects, and will also perform the SIPS and CGI and GAF weekly while in the study to follow clinical status.

Risks and Discomforts Associated with Compound LY404039 in Humans

A breakdown product of POMA, called LY404039, has been given to 24 healthy people in a previous study. Experiences reported by 2 or more people who have taken LY404039 were headache, feeling dizzy upon standing up, stomach pain, nausea (feeling sick to the stomach), sore throat, tiredness, or feeling sleepy.

Risks and Discomforts Associated with LY2140023 (Pomaglumetad, “POMA”) in Animals

POMA has been studied in animals. Rats treated with POMA showed uncoordinated movement, problems with walking, reduced body weight, uncontrollable and rapid shaking (convulsions or

possible seizures), or death. In 1 out of 40 rats treated with very high doses of POMA for 6 months, areas of brain injury were observed. Mice treated with POMA also showed uncontrollable and rapid shaking (convulsions or possible seizures). Vomiting, soft or watery stools, and/or a severe rash were seen in monkeys given high doses of POMA for up to 1 year. A single monkey was euthanized due to severe skin rash on Day 235 of the 1-year study. No convulsions have been observed in monkeys. In a study of the effects of POMA on pregnant rats and their offspring, some baby rats had significant decreases in their body weight, and some baby rats died up to 14 days after birth. The levels of drug in subject's blood will be lower than the levels of drug in monkeys at which the above bad effects were noted. Effects of convulsion observed in rats and mice were observed at blood drug levels that are similar to or lower than the levels expected in this study.

Summary

Doses of POMA as high or higher than the highest dose in this study (160 mg twice a day) have been taken by 24 healthy people without psychiatric illness for 10 days in a previous study without significant side effects. 44 patients with schizophrenia completed a multiple dose escalation study over a dose range of 160 to 480 mg BID for 7 days. Therefore, this dose and higher has been given before, but not for this length of time (14 days, though 7 and 10 days have been given).

2) Interviews and ratings (general): Study participants may feel anxious during medical history interviews or during administration of specific rating scales.

3) Brain imaging scans (general): It may be uncomfortable to lie motionless in the MRI scanner and it may cause some subjects to feel anxious.

4) Intravenous catheter: Intra-venous lines can cause pain, bleeding, or occlusion/clotting.

5) MRI Imaging: The Magnetic Resonance (MR) scanner uses strong magnetic fields and radio waves to take measurements in the brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the procedure, we will determine that patients do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and they will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). In addition, they will complete a brief interview at the time of study inclusion to determine if they have Asthma or a history of renal failure that may exclude their ability to receive an injection of Gadolinium (see below section). These questions will be repeated on the day of the scan.

For the scanning procedure, they will be asked to lie flat on the back in the MRI scanner for approximately 60 minutes and to remain as still as possible. Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for

pacemakers, some types of metallic implants, and medication patches, we are not aware of any other potentially dangerous interactions or hazards associated with the MRI scan. The MRI scanner also produces a loud noise.

6) Gadolinium compounds do have side effects, we use Dotarem. One side effect of gadolinium is nausea and vomiting, observed in less than 2 people out of every 100 injected. (1.8% estimate). Dry mouth (less than 2%), dizziness (0.7% up to 3.6%), and headache (2.2% up to 5.8%) are infrequent, yet possible side-effects. An additional side effect is hives, observed in less than 1 person out of every 100 injected with gadolinium. All of these side effects resolve within 20 minutes to several hours. People with asthma or known sensitivities to contrast agents are at increased risk for more serious side rare side effects (less than 1/10,000 injections estimate), such as severe allergic reaction that may result in sudden difficulty breathing, and therefore will not be injected with Gadolinium. Some patients with acute renal failure or end-stage renal disease have developed a serious medical condition known as nephrogenic systemic fibrosis (NSF) after the use of gadolinium for MRI. The primary concern regarding risks to renal function from gadolinium-based contrast agents (GBCAs) is specific to this population of patients who have end-stage renal disease (ESRD) on hemodialysis, or acute, florid, clinical renal failure, and then are exposed to gadolinium. This population of patients is by definition excluded from this study by virtue of medical history and general review of systems. Renal dysfunction as a result of gadolinium in a population without history of end-stage renal disease or acute renal failure has not been described in the medical literature. In a retrospective study conducted at two large medical centers, 74,124 patients were injected with a standard dose of gadolinium (0.1mmol/kg, the same dose used in our research studies) who had no screening for renal function, with a rate of zero/74,124 cases of renal complications (e.g., nephrogenic systemic fibrosis (NSF) or other renal dysfunction) post injection (Prince, Zhang et al. 2008). All 15 cases of NSF that were found in this retrospective study all had severe, clinical renal failure at the time of gadolinium injection. No cases of NSF have been identified in persons with normal renal function or with moderate renal dysfunction.

Regarding this specific risk, the FDA recommends:
1. Become familiar with the patient populations at risk for NSF.
2. Avoid using gadolinium in patients with known risks for developing NSF.
3. Prior to administering gadolinium, evaluate patients for renal dysfunction by assessing their renal function, either by obtaining a medical history or conducting laboratory tests that measure renal function.
4. When administering gadolinium, do not exceed the recommended dose in product labeling and allow a sufficient period of time for elimination of the agent from the body prior to any further gadolinium administration. The American College of Radiology recommends, as of July 2007, pre-screening patients prior to the administration of Gadolinium-Based MR Contrast Agents (GBMCA) their glomerular filtration rate (GFR) for the following patient groups:

1. Renal disease (including solitary kidney, renal transplant, renal tumor)
2. Age >60
3. History of Hypertension
4. History of Diabetes
5. History of severe hepatic disease/liver transplant/pending liver transplant. For patients in this category only, it is recommended that the patient's GFR assessment be nearly contemporaneous with the MR examination for which the GBMCA is to be administered. Concurrently, researchers investigating clinical

risk factors as well as the role of gadolinium formulation in development of NSF (Peak and Sheller 2007; Kanal, Broome et al. 2008) note that the Gadolinium-based contrast agents may possess differential risk of NSF depending upon their chemical structure. Gadolinium agents are classified on the basis of chelate biochemical structures (macrocyclic vs linear) and chelate charge (ionic vs nonionic) (Perazella 2007). Macrocyclic molecules bind gadolinium more tightly than do linear chelates, possess high thermodynamic conditional stability, and have lower dissociation rates. Ionic cyclic chelates are thought to be the least likely to release free gadolinium, whereas nonionic linear chelates are the most likely to release free gadolinium in the body. Risk of NSF is considered to be the highest with Omniscan and OptiMARK, which carry no molecular charge, are arranged in a linear structure with excess chelate, and seem more likely to release free gadolinium into the body. Since gadodiamide (Omniscan) has been most commonly associated with NSF(Thomsen 2006) and gadopentetate dimeglumine (magnevist) second-most associated ; the Neurological Institute's imaging center has changed contrast agents from Omniscan to Dotarem, a macrocyclic ionic agent.

The dosing guidelines for the brand of gadolinium to be used in this study are as follows: CNS (Central Nervous System) Adults: The recommended dose of Dotarem 0.1mmol/kg (0.2 mL/kg) administered as a rapid bolus intravenous injection. According to the Multihance package insert and the recent literature, repeated dosing of mutihance up to a total dose of .3mmol/kg (in three doses of 0.1mmol/kg) can be immediate given within a short time-span with no adverse effects. The elimination half-life of the compound is 1-2 hours. Prior to readministration, the FDA recommends 'sufficient time for drug elimination'. Our study design of a single baseline dose at 0.1mmol/kg followed by repeated injection 2 weeks later is more than adequate time for elimination of contrast agent, which should be complete by two days, and is well below the maximal dosing guidelines that have been shown to be safe with repeated dosing in prior studies.

COVID Risks There is a risk of exposure to COVID when deciding to go out in public and travel for research.

Describe procedures for minimizing risks

1) POMA: In order to minimize risk, we will exclude any individual with any history of seizure disorder, or any severe medical condition. We will obtain frequent laboratory analyses, including liver tests, and cbc, adverse event queries, and EKGs and temperature during this study. Patients will be terminated from the study if they develop side effects that are, in the opinion of the PI, preclusive of continuing in this protocol or in particular if they meet worsening criteria based on the CGI or need for prn medications.

2) Interviews and ratings (general) Participants will be allowed to take breaks as necessary and are not required to answer any questions that may be uncomfortable.

3) Brain imaging scans (general): Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the MRI magnet bore if requested.

4) Intravenous catheter: Placement risks are minimized by using proper techniques.

5) MRI Imaging: Before beginning the procedure, we will determine that patients do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and they will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). In addition, they will complete a brief interview at the time of study inclusion to determine if they have Asthma or a history of renal failure that may exclude their ability to receive an injection of Gadolinium (see below section). These questions will be repeated on the day of the scan. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. If a patient experience any discomfort and wish to stop the scan, he/she can tell the MRI technologist who will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

6) Gadolinium -A trained physician will inject the gadolinium and remain with the patient for the entire duration and for 15minutes after the scanning session is complete. Prior to scan, all participants being considered for participation in this study will continue to have a complete medical history prior to MRI to screen for renal failure/history of renal disease, diabetes, or hypertension, as well as screening labs. Patients with a diagnosis of acute renal failure are invariably severely medically ill and hospitalized, and are not eligible for study participation. In the current protocol, we administer Dotarem according to the patient's weight at a dose of 0.1mmol/kg. Based upon the amount administered, we do not exceed the recommended dosage. In addition, an Epi Pen will be available at all times during scanning with gadolinium.

COVID Risks: We will instruct subjects to wear a mask in public and while traveling, practice hand hygiene, and stay at least 6 feet away from others. We will tell subjects that if they do not feel comfortable traveling to the medical center for an appointment, for example if the subway or bus they would normally take is crowded, they can reschedule, or we may be able to arrange alternative transportation (if it is the case that alternative transportation, such as Uber or Lyft, can be offered). We have also minimized in-office visits to lessen this risk. We will keep our subjects informed about current public health recommendations, such as federal and local government guidelines and directives.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All records of the participating subjects will be kept in a locked room with access provided only to staff members. All data collected will be kept confidential and used for professional purposes only. Publications using these data will be done with only deidentified data. As this study is an intervention study utilizing an IND there is a possibility that the FDA will inspect our records.

When done remotely, we will use redcap to obtain consent on the cfs and hipaa forms. When sending electronic messages to subjects, we will only use encrypted email (NYSPI encrypted) and when

sending attachments with PHI only use the NYSPI secure file transfer website (https://attach.nyspi.org/) or encrypted nyspi email or redcap.

When COPE staff work from home, we all use the nyspi onedrive sharepoint system for storing documents or HIPAA compliant storage devices for paper documents. When conducting remote visits, we will use telephone or hipaa compliant video conferencing.

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are no direct benefits for participating patients.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

Subjects will receive $50 per visit, not including MRI, up to 5 total visits (up to 3 for screening, day 7, day 14). In addition, patients will receive $150 for participation in each MRI imaging with gadolinium contrast (up to 2). Subjects will also receive reimbursement for local transportation. Payments will be made in cash or check. The total estimated compensation for this study is approximately $550.

For the test retest study, healthy subjects will receive $50 for their screening visit, not including MRI, and $100 for participation in each MRI imaging with gadolinium contrast (up to 4). Subjects will also receive reimbursement for local transportation. Payments will be made in cash or check. The total estimated compensation for this study is approximately $450.

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