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Subject's Name:
Title of Research Protocol: **Proof of Mechanism Study using a Retinal Biomarker to Predict Treatment Response with Intravenous Sodium Nitroprusside in Symptomatic Early Course Schizophrenia**
Principal Investigator's Name: **Paulo Lizano**
Protocol #: **2021P000535**

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

Subject's Name:
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Principal Investigator: Paulo Lizano MD, PhD
Protocol Number: **2021P-000535**

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

Why am I being invited to take part in a research study?

You are being invited to take part in the research study because you are someone with minimally treated clinically stable early course schizophrenia spectrum disorders. These disorders vary in degree of presentation of the features of the disease. However, they typically include a change of thought and behavior which leads to distorted interpretation of reality. The proposed study will examine the therapeutic benefit of intravenous sodium nitroprusside (SNP), a medication used to lower blood pressure, in early course schizophrenia spectrum disorders.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- Your participation is completely voluntary.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- Your refusal to participate will not result in any consequences or any loss of benefits that you are otherwise entitled to receive.
- You can ask all the questions you want before you decide.
- If you choose not to take part, or if you leave the study, your decision will in no way harm your relationship with any member of the research team or any other individuals at BIDMC

Why is this research being done?

The main purpose of this study is to explore whether a single infusion of SNP, a medication that is mainly used for high blood pressure, can improve positive and negative symptoms of psychosis in early course schizophrenia patients. An additional goal is to investigate the role of retinal and peripheral inflammatory markers of microvascular dysfunction as predictors of treatment response to SNP in early course schizophrenia.

How long will the research last and what will I need to do?

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We expect that you will be in this research study for up to 4-weeks for clinical assessments, retinal imaging, blood marker assessments, urine test and treatment with either intravenous SNP or placebo. We will have a virtual clinical assessment visit prior to the first in-person visit to determine eligibility for this study. The rest of the visits will be split up into a baseline, week 1, week 2, and week 4 visits. Each time point in the study can take up 1-2 visits.
Visits will include assessments and tests which take different amounts of time: Clinical assessments take approximately 1-2 hours each, retinal imaging studies take approximately 2-5 minutes each, blood and urine test take approximately 5 minutes each, drug infusion take 4 hours.

You will be asked to take part in clinical as well as retinal imaging and blood marker assessments. You will also be asked to go to Massachusetts Eye and Ear for retinal blood vessel imaging using optical coherence tomography angiography (OCTA) and BIDMC to get a physical examination, collection of urine drug, pregnancy and blood tests, and electrocardiogram (EKG). You will need to come to BIDMC Clinical Research Center to get treatment with either SNP or placebo. If your clinical, urine drug or pregnancy tests are indicative of our exclusion criteria (positive pregnancy, positive drug test, unstable medical issue etc.) then we will have to exclude you from the study at that time.

More detailed information about the study procedures can be found under ***"*DESCRIPTION OF STUDY DETAILS*".***

Is there any way being in this study could be harmful to me?
There is a potential for questions in the standardized interviews that may be embarrassing or upsetting. Staff will be sensitive to these issues and will not demand sensitive issues to be discussed.

OCTA is painless and safe technique that will be used to investigate the structure and function of the retina. You may have your pupils dilated for OCTA retinal imaging, which may result in light sensitivity or acute angle closure glaucoma. The risks and discomforts of blood drawing from a vein include the possibility of pain or bruising at the site of the blood draw; occasional feeling of lightheadedness; and rarely, infection at the site of the blood draw.

Single infusion SNP has been demonstrated to be safe and well-tolerated in previous studies. Side effects may include hypotension which mostly resolves quickly. Cyanide toxicity is possible with much higher dosages of SNP, but otherwise the risk is minimal.

More detailed information about the risks can be found under ***"*RISKS AND DISCOMFORTS*".***

Will being in this study help me in any way?
We cannot promise any direct benefits to you or others from your taking part in this research. However, by participating in this research, you will contribute to the possible benefits of SNP as well as contribute to the understanding of how SNP may result in changes in the eye and brain.

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What happens if I do not want to be in this research?
Participation in research is completely voluntary. You can decide to participate or not to participate in the study. Your alternative to participating in this research study is to not participate. You will be able to withdraw from the study at any time you want.

DETAILED INFORMATION SECTION
Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand. Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of the form to keep for your records.

DISCLOSURE OF SPECIAL INTERESTS OF BETH ISRAEL DEACONESS MEDICAL CENTER AND INVESTIGATORS
This study is being conducted by Paulo Lizano, MD/PhD and is funded by Alkermes and Internal Funds. The funding agency in this study, Alkermes and Internal Funds, is paying BIDMC and Dr. Paulo Lizano to perform this research. Neither BIDMC nor Dr. Lizano have any additional interests in this research project.

WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS
If you have any questions, concerns or complaints about this research or experience any problems, you should contact Dr. Paulo Lizano at [617] 754-1227.

PURPOSE
You are invited to take part in a clinical trial at BIDMC and Mass Eye and Ear (MEE) to evaluate the effectiveness of a single intravascular administration of the study drug, sodium nitroprusside (SNP) (0.5 µg/kg/min for 4 hours) compared to placebo on positive and negative symptoms in Early Course Schizophrenia. This study's secondary objective is to examine the effect of SNP on cognitive processing such as thinking, memory, language, judgment, and retinal vessel measures, and whether baseline retinal vessel measures or blood inflammation measures correlate with a change in psychosis symptoms or cognition. The retina is a thin layer of tissue that lines the back of the eye on the inside. We are evaluating these vessels because they reflect the brain vessel condition.

The drug involved in this study; Sodium Nitroprusside is investigational. This means that the study drug is still being tested in research studies and is not approved by the Food and Drug Administration [FDA] for the way that it is being used in this study. This particular investigational agent, Sodium Nitroprusside, has been approved by the FDA for use in other diseases or conditions, but we do not yet know if it is useful or safe as a treatment for early course schizophrenia spectrum disorders.

STUDY PARTICIPANTS
You have been asked to be in the study because you have been diagnosed with early course schizophrenia spectrum disorder with little exposure to antipsychotic medications, Approximately 32 people will take part in this study at BIDMC. There will be 16 people randomized to SNP treatment and 16 to placebo treatment.

DESCRIPTION OF STUDY DETAILS

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If you agree to be in this study, you will be in this research study for 4 weeks.

Because individuals who are recruited for this study display symptoms of psychosis, we will also be implementing an Assessment of Capacity form to assess interested participants ability to consent to the study. This form assesses your ability to understand and willingness to choose to participate in this study. An individual on our study team who is qualified to administer an Assessment of Capacity form will complete this form with you.

After you sign the consent form, the following things will happen:

Screening Procedures: Screening procedures are tests and procedures that will be completed to determine if you are eligible to take part in the research study. All participants will undergo these screenings. For this research study, the screening procedures include:

- your age, gender, race, ethnicity, and education
- your psychiatric history and symptoms you may have had throughout your life
- your social history (friendships and social activities) and your work history
- psychiatric symptoms you may be experiencing currently
- your family psychiatric history
- your history, and how you are feeling currently.
- your medical history, including cardiac, renal or vascular disease.
- your medication allergies to see if it is safe for you to be administered SNP.

If you undergo a remote consent process (1 hour), the screening procedures listed above will occur virtually over Microsoft Teams before your first in-person visit.

- You will have a urine test for drugs of abuse at MMHC or BIDMC (you will not be able to participate in this study if urine test for drugs comes back positive). In cases of remote consent, the drug screen will occur at the start of the participant's first in-person visit. You will be informed that, if you have a positive drug test, you will be excluded from the study at thattime.
- Women of child bearing potential will have a urine pregnancy test. If you are pregnant or breast feeding, you will not be able to participate in this research study. Pregnancy is a strict exclusion criterion for study participation; should you become pregnant over the course of the study, you will be asked to leave the study without any adverse consequences. In the case of a remote consent, the pregnancy test will be administered during the first in-person visit. You will be informed that, if you have a positive pregnancy test, you will be excluded from the study at that time.

Your results on any of the above questions and tests will not be disclosed outside of the study without your permission. If at any point these questions make you uncomfortable, you may choose not to answer them or ask to stop with the procedures or questionnaires.

Medical Screening: If you meet criteria for the study, you will undergo a physical examination, vital sign collection, routine laboratory tests (CBC with differential, CMP, TSH, CRP, Lipid panel and serum pregnancy test if appropriate), and 12-lead EKG to ensure medical stability.

Blood Collection: The purpose of the blood sample collection is to look for variations in your blood that can help

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identify predictors of response to SNP. Your blood sample will be saved for scientific analyses that will be done in the future. Up to 7 tablespoons (100ml) of blood will be drawn from a vein in your arm with a small sterile needle. This is the standard method used to obtain blood for routine hospital tests and will be conducted by trained clinical research center personnel at BIDMC. Blood will be collected at baseline, week 2 and week 4. We may ask for a second blood sample if the research laboratory cannot process the first sample.

Clinical and Cognitive Testing: If you meet criteria for the study, you will be assessed for symptoms of psychosis and functioning at baseline, hour 2, and hour 5 after drug infusion, as well as week 1, week 2, and week 4. You will also complete electronic (GoogleForm), paper/pencil, and iPad assessments that will test your attention, memory, and problem solving. This will take about 1 hour. These tests will be conducted at baseline line, week 1, week 2, and week 4.

OCTA Procedures: If you qualify to take part in this research study, we will perform an examination of both of your eyes at the MEE (800 Huntington Ave, Boston, MA 02115) prior to the infusion (4th) visit. This would be just like visiting any eye doctor for a general eye examination. We will then take color photographs of your retina in both eyes to document our exam findings. We will also then check optical coherence tomography angiography (OCTA) imaging twice to evaluate your retina at the sametimes with the eye examination. This involves sitting at a tabletop device and looking through the eye piece for 5 minutes while images are taken of both eyes. All these tests are standard of care imaging tests in a retina practice, are FDA-approved, and represent no additional risk to your general eye health. We will not perform pupil dilation, but in situations when high quality retinal images cannot be obtained, we may consider performing pupil dilation.

Randomization Procedures:

Randomization Procedures:

It is not clear at this time which of the treatments *drugs* in this study would be better for you. For this reason, the treatment plan offered to you will be picked by chance [like the flip of a coin]. You will not be able to choose which treatment you receive. The chances of receiving either of the treatments are approximately equal. After the randomization, you will be assigned to one of the following groups:

A) Experimental: Sodium Nitroprusside Arm

B) Placebo Comparator: Placebo Arm

If one treatment arm is found to be less effective then the other while you are taking part in the study, you will be informed and further treatment will be discussed.

Placebo:
Depending upon the group to which you are assigned, you may receive a placebo instead of the study drug. A placebo is an inactive pill that looks like the study drug,

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but a placebo contains no active medication. Placebos are used to help determine if the results of the study are truly from the study drug. You will not know whether you will be receiving the study drug or the placebo. However, this information can be learned in case of an emergency.

You will be randomized to receive SNP or placebo (5% glucose) infusion. Neither you nor your investigator will know which drug you are receiving. However, this information can be learned in case of an emergency. Experimental infusion standards and conditions will be identical for both infusion groups, and both patients and study staff will be masked to the assigned intervention.

Research Procedures:

If you qualify to take part in this research study, you will undergo these research procedures:

- SNP infusion will take place at the BIDMC Clinical Research Center, 8th floor – Feldberg and Gryzmish Buildings, 330 Brookline Avenue GZ-800, Boston, MA 02215.
- A single dose of 0.5 μg/kg/min SNP or placebo (5% glucose solution 0.5 μg/kg/min) will be infused over 4 hours.
- You will be recumbent on an infusion chair for the entirety of the infusion.
- A member of the study will review any side effects, health, or medication changes with you before and after the infusion.
- A staff of the Clinical Research Center will prepare the medication bag and the infusion equipment. A tourniquet will be tied to your arm to locate the vessel. The cannula for the infusion will be inserted in a vein on your arm. As the cannula is inserted you may feel stinging sensation due to the needle.
- The medication will be infused through this cannula for 4 hours. Once the infusion is completed, the cannula will be removed, and a plaster will be stuck in your arm. Pressure on your insertion area for a few minutes may be needed at the end of the infusion.
- The staff will be monitoring you during the entire process.
- You may complete a few assessments on the scope of the research after the infusion. Assessments are explained below, in the “Monitoring/Follow-up Procedures” part.
- We will check in with you throughout the study to see if you are having any trouble with the study schedule or procedures or have any questions or concerns.

Monitoring/Follow-Up Procedures. Procedures performed to evaluate the effectiveness and safety of the research procedures are called “monitoring” or “follow-up” procedures. For this research study, the monitoring/follow-up procedures include:

- Your blood pressure, heart rate, blood oxygen saturation, and EKG results will be continuously monitored during the infusion. The monitoring will be performed by Clinical Research Center staff.
- Dr. Katherine Berg, a Critical Care Physician at BIDMC will be the doctor of record and will be providing medical clearance and providing oversight for the infusion of SNP.

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- You will undergo PANSS (Positive and Negative Symptom Scale) assessment (baseline visit, after infusion: time 0hr, 2hrs, 5hrs, 1wk, and 4wks), overall cognition assessment using the Brief Assessment of Cognition in Schizophrenia App (time 0hr, 1wk, 2wks, and 4wks), and retinal imaging (time 0hr, 5hrs). You will complete your final follow-up study visit at day 28 (4wks), including clinical, safety, and EKG assessments. These assessments will be performed by the research team.
- You will undergo blood collection at baseline, week 2, and week 4.

Table 2: Study schedule.

Study Visit Timeline	Screening visit	1st In person visit	Infusion visit	Week 1 visit	Week 2 visit	Week 4 visit
Assessment of Capacity/Consent	X					
Clinical Evaluation	X	X	X	X	X	X
Retinal Imaging (0hr, 5hr)		X	X			
Urine toxicology screen		X				
Urine Pregnancy Test (for women of childbearing potential)		X				
Blood test (0hr, 2wk, 4wk)		X			X	X
PANSS (0hr, 2hr, 5hr, 1wk, 2wk, 4wk)		X	X	X	X	X
Brief Assessment of Cognition in Schizophrenia (0hr, 1wk, 2wk, 4wk)		X		X	X	X
SNP infusion (4 hours)			X			
Clinical Follow-up			X	X	X	X

We, the BIDMC research team, may want to contact you in the future.

- We may contact you to obtain additional samples or to request updates on your health. If we ask, keep in mind you are under no obligation to donate additional samples or provide additional information.
- We may send periodic notifications about the types of research being done with your samples/data, and

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about the scientific and medical progress that has been made.

- Please remember to update BIDMC research team with your contact information if it changes. Otherwise, they may not be able to find you.

Remember that you can re-contact the research team at any time, now or in the future, and ask any questions you have.

With this consent form, you are asked to agree to be re-contacted by the researchers in the future for a variety of reasons. However, if you do not wish to be re-contacted, please indicate your preference below:

_____Check and initial here if you DO NOT agree to be re-contacted in the future by the research team for any reason.

Individual Research Results
Your study doctor will disclose any clinically relevant research results to you, including incidental findings.

Most tests done on samples in research studies are only for research and have no clear meaning for health care. The research testing done in this study is a steppingstone to learning more about psychosis.

While you should not expect to receive any results from the research testing, if we find that research results from your sample are of high medical importance, we may attempt to contact your medical provider to discuss the results. In some situations, follow up testing might be needed in a Clinical Laboratory Improvement Amendments (CLIA) certified clinical lab. You and your medical insurer may be responsible for the costs of these tests and any follow up care, including deductibles and co-payments. It is possible that you will never be contacted with individual research findings. This does not mean that you don't have or won't develop an important health problem

Information and Biological Samples
Your information and biological samples will be used and shared with the sponsor and the researchers involved in this study to conduct the research. The consent form provides information on who will have access to identifiable information and identifiable biological samples during the study. We also want you to know that your information or biological samples may be stripped of any identifiers (for example your name, medical record number or date of birth) and used for future research studies or distributed to another researcher for future research studies without additional informed consent. BIDMC researchers or other third-party researchers may use your information and samples in other scientific research, product testing or commercial development. It is unknown whether a product will ultimately be developed from the research described in this consent form or from any such work that may be performed by BIDMC or other third parties receiving your information or biological samples. In signing this consent form, you are acknowledging and voluntarily consenting to the possibility that your information and biological samples may be used for commercial purposes. For example, your samples and information may be used to develop a new product or medical test to be sold. BIDMC and other researchers may benefit if this happens. There are no plans to pay you if your samples and information are used for this purpose.

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If your identifiers are removed, we will not be able to destroy or remove your information or biological samples from distributed information or samples. As part of this research program and as further explained in this form, samples of your tissue and/or information about your medical history may be provided to other researchers and/or outside collaborators.

Storing of Identifiable Information and Samples for Future Use
At the completion of this research, we would like to store any remaining sample(s) and information collected from or about you for this research for possible future use. Your sample will be stored with identifiers, such as your name or medical record number. The remaining samples and information may be stored indefinitely and may be used for future research of psychosis. The research staff will have a list to know which sample is linked to which participant and this list will be kept confidential in a secure location. If the research investigator distributes your samples to other researchers or institutions, they will be labeled with a research code without identifiers so that you cannot be identified by the other researchers or institutions.

If you have questions about storing samples or information or would like to request that samples or information, be removed from storage, please let us know. It is not always possible to remove samples or information from storage or to retrieve samples or information that have/has already been sent to other investigators.

I agree to allow my samples and information to be stored and used for future research as described above: (please check and initial one to indicate your choice)

_____ YES _____NO

RISKS AND DISCOMFORTS

As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

Potential Risks and Discomforts to Subjects: Participants on treatment will be allowed to continue their prescribed medications. If symptoms worsen or new symptoms emerge requiring active therapeutic intervention, the study psychiatrist (Dr. Lizano, the PI) will ensure appropriate intervention and referral.

Psychological Interview: There is a possibility that a patient may become distressed when being asked about symptoms or personal information during the diagnostic evaluation or assessment session. The primary risks to the patients are discomfort or anxiety. Subjects may also experience some discomfort or anxiety from discussing personal information. Yet this anxiety is not expected to be greater than that subjects already experience and subjects will be assured that they will be able to withdraw from the study at any time. There is a possibility of suicidal ideation as a result of any anxiety or distress associated with discussing personal information. This risk is largely reduced by screening out patients with significant suicidal ideation or those who have enacted suicidal behaviors within 6 months prior to intake.

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Cognitive Tests: The cognitive tasks pose no risks to participants. The tasks will require sustained attention and mental effort for a steady period of time. This could lead to minor temporary fatigue or boredom, but otherwise there are no known risks. We will ensure that data remain as confidential as possible. Also, these data generally are not considered to be of sensitive nature.

SS-OCTA: OCTA is painless and safe techniques that will be used to investigate the structure and function of the retina. Performing these imaging techniques in individuals with psychotic disorders does not pose specific, additional unique challenges or risks to the participants. Participants will have their pupils dilated for OCTA retinal imaging, as is done with all ophthalmology imaging facilities. When possible, we will forgo pupil dilation, especially when high quality retinal images can be obtained without the need for pupillary dilation.

Rare: If your pupils are dilated for this study. You may expect to experience the following:

- Blurred vision for 2-3 hours, particularly with reading
- Sensitivity to bright light until the drops wear off (2-3 hours)

BIDMC will provide reimbursement for transportation to and from your study visit. We will give you sunglasses to wear on the way home to reduce discomfort from the bright light.

Rare. There is a very rare chance of the eye drops closing off the area of the eye that allows fluid inside the eye to drain (acute angle-closure glaucoma). Acute angle closure would occur within the first 24 hours after we put the eye drops in your eyes. If this happens, you might experience sudden eye pain. It is important to contact the Doctor or visit the emergency room if you experience sudden eye pain.

Blood draw: Temporary irritation from the needle stick, the likelihood of pain or bruising at the site of the blood draw, occasional symptoms of lightheadedness, and, in rare cases, infection at the site of the blood draw are all risks and discomforts associated with blood draw procedure.

IV infusion of SNP: IV treatment is relatively safe, there can be complications if not administered properly. The most common complications include phlebitis, extravasation, air embolism, infection.
The single administration of IV Sodium nitroprusside has been reported to be safe and well tolerated. The most important adverse reactions are the avoidable ones of hypotension and cyanide toxicity and other side effects reported as; bradycardia, tachycardia, palpitations, headache, increased intracranial pressure, skin rash and nausea. The potential for cyanide toxicity is greatest when more than 500 g/kg of sodium nitroprusside is administered faster than 2 g/kg/min, as cyanide is generated faster than the unaided patient can eliminate. Cyanide toxicity will be avoided in this study as the dose administered is very low, and individuals with renal impairment will be excluded. Also, the study treatment will be infused within 3-12 hours of preparation as sodium nitroprusside is only stable in solution for 24 hours. The infusion protocol will be 0.5mcg/kg/min which is the minimum therapeutic dose and patients will be continuously monitored during the infusion. The infusion procedure will take place at the Clinical Research Center at BIDMC, which is a fully staffed center with nurses and physicians, as well as all the necessary monitoring and personal protective equipment. In 4 other similar studies with the same protocol, there were no serious side effects.
Sodium nitroprusside does have some potential for drug-drug interactions. The hypotensive effect of sodium nitroprusside is augmented by that of most other hypotensive drugs, including ganglionic blocking agents, negative inotropic agents, and inhaled anesthetics. Subjects taking any of these drugs will be excluded from

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the study. Patients will also be advised not to take these medications during the study.

Potential Side Effects;

- Low blood pressure; SNP can cause low blood pressure leading to hypoperfusion of vital organs. Hypotension should resolve within 1-10 minutes after discontinuation of the nitroprusside infusion; during these few minutes, it may be helpful to be in a head-down (Trendelenburg) position to maximize venous return.
- Cyanide Poisoning SNP infusions above 2 μg/kg/min generate cyanide ion (CN-) faster than the body can normally dispose of it. At the maximum recommended infusion rate of 10 μg/kg/min, the patient's ability to buffer CN- will be exceeded in less than one hour. Patients with liver dysfunction are more susceptible to cyanide toxicity.
- Thiocyanate Poisoning Most of the cyanide produced during metabolism of SNP is eliminated in the form of thiocyanate. Thiocyanate is mildly harmful for nerve cells (ringing in the ears, constriction of the pupil of the eye, over activity of reflexes) at serum levels of 1 mmol/L (60 mg/L). Renal hemodialysis may be used to eliminate thiocyanate in cases of severe poisoning.
- Increased Methemoglobin levels; SNP infusions cause conversion of hemoglobin to methemoglobin in a dose-dependent manner. Methemoglobin binds oxygen more strongly than does hemoglobin, and when methemoglobin levels are elevated, oxygen release from red blood cells in tissue capillaries may be impaired. However, conversion of methemoglobin back to hemoglobin is normally rapid, and clinically significant increase in methemoglobin is infrequent. Suspect methemoglobin elevation in patients who have received >10 mg/kg of SNP and who exhibit signs of impaired oxygen delivery despite adequate amounf of blood pumped from the heart and adequate arterial oxygen pressure. Blood with increased methemoglobin levels is chocolate brown, without the expected color change on exposure to air. Methemoglobin levels >10% are considered clinically significant. When methemoglobinemia (increased levels of methemoglobin) is diagnosed, the treatment of choice is 1-2 mg/kg of methylene blue, administered through a vein over several minutes.
- Increased Pressure Within Skull; Like other drugs for vessel dilatation, SNP can cause increases in pressure within skull.

Less common adverse reactions include**:**

Cardiovascular: abnormally slow heart action, changes in electrical signals of the heart, abnormally fast heart action, heart pounding, discomfort behind the breastbone
Dermatologic: Rash
Endocrine: : Low thyroid hormone levels
Gastrointestinal: Interrupted movement of the intestine, nausea, abdominal pain
Hematologic: Decreased platelet function which could cause tendency to bleed
Musculoskelatal: Muscle twitching
Neurologic: Increased intracranial pressure, dizziness, headache
Miscellaneous: Redness in the skin, excessive sweating, varicose vein, irritation at the infusion site

If you are pregnant or become pregnant, this treatment may involve risks to the embryo or fetus which

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are currently unforeseeable.

- Pregnancy: Based on animal data and mechanism of action, SNP may lead to cyanide exposure and potential adverse effects in the fetus. Published post-marketing reports with SNP use in pregnant women are insufficient to inform a drug-associated risk of adverse pregnancy related outcomes. There were no animal reproduction studies conducted with SNP during pregnancy. However, there are published studies in pregnant sheep that demonstrate that nitroprusside crosses the placenta and that fetal cyanide levels were dose-related to maternal levels of SNP. Advise pregnant women of the potential risk to a fetus.
  - The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
  - Prolonged use and large doses of SNP during pregnancy may result in cyanide toxicity that may be fatal to the fetus. In the unusual case that there is no appropriate alternative to therapy with SNP for a particular patient, apprise the mother of the potential risk to the fetus.

Loss of confidentiality

There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information. However, if your participation becomes known, it could create a problem or hardship for you depending upon the type of information disclosed.

CONFIDENTIALITY
Information learned about you during this research program will be maintained confidentially by the research staff as described in this form.

Information learned from your participation in this study and from your participation may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, the Committee on Clinical Investigations, the Human Subjects Protection Office and others involved in research administration of the BIDMC with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

Massachusetts law requires that certain trained individuals (mandated reporters) disclose to the proper authorities any information shared with them about abuse of the elderly, abuse of mentally ill or developmentally disabled persons, child abuse, or child sexual abuse. Many of the clinicians meeting with you are mandated reporters. The investigators may also be required by law to report threats of harm that you make, either to yourself or to others.

MEDICAL RECORD

Information from this study will not be placed in your medical record.

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Principal Investigator's Name: **Paulo Lizano**
Protocol #: **2021P000535**

POSSIBLE BENEFITS
It is not possible to predict whether you will benefit directly from participation in this study. However, your participation may help others in the future as a result of knowledge gained from the research. However, as shown by previous clinical studies, an immediate improvement in overall psychosis and negative symptoms in participants with Early Course Schizophrenia may be achieved with SNP treatment.

OTHER AVAILABLE OPTIONS
Taking part in this study is voluntary. You have the right to decide not to take part in this study.
This research study is not meant to diagnose or treat medical problems. Participation in this research study does not take the place of routine physical examinations or visits to your regular doctor.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY
Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. Your decision to not participate will not result in any penalties or loss of benefits to you. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with the research team or any other individual at BIDMC.

INVESTIGATORS RIGHT TO STOP THE STUDY
The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU
Costs Covered by Study
You will not be charged for baseline tests, SNP or placebo (5% glucose) infusion or follow up tests/measures.

Payments to You:
You will be paid up to $300 if you complete all parts of the study. The breakdown of payments is detailed as followed:

1. $50 for screening visit and consent.
2. $125 for completing the infusion visit (second in-person visit) which includes single IV drug infusion and assessments before, during and after the infusion.
3. $125 for completing 1 week, 2 week, 4 week follow-up visits which include clinical exams, cognitive assessments, blood collections.

You will be reimbursed for the following: travel and/or meals up to $10.

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The amount of reimbursement will be based on receipts for these expenses. It may take up to 8 weeks for you to receive payment by check.

Any payments made to you may be taxable income to you. This does not include any payments you may receive to reimburse (pay you back) you for certain expenses like parking fees or travel. We are required to obtain your name and social security number for preparation and submission of Internal Revenue Service (IRS) Form 1099-Misc. You may receive an Internal Revenue Service Form 1099 from BIDMC if you receive more than $600 or more in one calendar year for taking part in one or more research studies at BIDMC. Questions about your own tax status should be referred to your personal tax advisor.

For this study, compensation may be provided through an electronic payment card (like a pre-paid debit card) called the ClinCard Program, if you choose to do so. The ClinCard Program is provided to BIDMC by a third-party company called GreenPhire. You will be issued a Greenphire ClinCard, which is a debit card that funds are loaded onto in connection with you taking part in this study. The study staff will provide you with additional information about how ClinCard works, including terms and conditions for the use of ClinCard. In order to complete your payments, Greenphire will need to process certain personal information about you: your name (required), birth date (required), address (required), and contact details (cell/mobile phone number and/or email address- optional for study related communications). This information will be collected from you by the staff in clinic and given to Greenphire. By agreeing to receive reimbursement for this study, you are authorizing the release of this information to Greenphire. By providing this information, Greenphire will be aware that you are enrolled in a clinical trial at BIDMC. Please allow up to three business days for payments to be credited to your ClinCard.

Cost of Research Related Injury:
If you are injured as a direct result of your participation in this study, you should contact the Investigator at the number provided under the section “Who to Call if You Have Questions” in this form. You will be offered the necessary care to treat your injury. We reserve the right to bill your insurance company or the sponsor, if appropriate, for the care you get for the injury. We will try to get these costs paid for, but you may be responsible for some of them. You may be responsible for all co-payments and deductibles required under your insurance. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

OTHER IMPORTANT INFORMATION
A description of this clinical trial will be available on www.ClinicalTrials.gov as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION
As part of this study, we will be collecting, using and sharing with others information about you. Please review this section carefully as it contains information about the federal privacy rules and the use and disclosure of your information.

Description of Protected Health Information [PHI]

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By signing this informed consent document, you are allowing the investigators and other authorized personnel to use and disclose health information about you. This may include information about you that already exists (for example: your medical records and other sources of health information, demographic information, the results of any laboratory tests, and mental health records if applicable as well as any new information generated as part of this study. This is your Protected Health Information.

People/Groups at BIDMC Who Will Share and Use Your Protected Health Information
Your Protected Health Information may be shared with and used by investigators working on this study, including the supporting research team (such as research assistants and coordinators, statisticians, data managers, laboratory personnel, pharmacy personnel, and administrative assistants), and may also be shared with and used by other health care providers at BIDMC who have treated you in the past and have information relevant to the research, or who provide services to you in connection with the research.

People/Groups Outside of BIDMC Hospital To Whom Your Protected Health Information Will Be Disclosed (Shared) and Who May Use Your Protected Health Information
We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this research study:

- The funding source and/or sponsor of this study is Alkermes, INC, where applicable, the people and companies that the funding source and/or sponsor use to oversee, administer, or conduct the research (for example, clinical research organizations are companies that are sometimes hired by research sponsors to help manage and run a clinical research study)
- The members and staff of Research Administration at BIDMC and the Committee on Clinical Investigations of BIDMC, which is responsible for reviewing studies for the protection of the research subjects, so that it can carry out its oversight responsibilities with respect to the study.
- MEE and research collaborators at the MEE.
- Other research collaborators and supporting research team members taking part in this study
- Any external health care providers who provide services to you in connection with this research
- Laboratories not affiliated with BIDMC that are involved in conducting tests related to the research
- Statisticians and other data monitors not affiliated with BIDMC
- The members and staff of any other IRBs (beyond the BIDMC Committee on Clinical Investigations) that oversee the research
- Centralized data collectors
- Your health insurance company
- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], the National Institute of Health [NIH], the Office for Human Research Protections [OHRP], and other federal and state agencies that may have jurisdiction over the research
- Hospital and Clinical Research Accrediting Agencies
- Data and Safety Monitoring boards that oversee this study (if applicable)
- Other outside laboratories
- Greenphire, the third-party organization through which ClinCard reimbursement is done.

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Those who receive your Protected Health Information during the course of the research may not be required by the federal privacy regulations to protect it, and they may make further disclosures to others and use your information without being subject to penalties under those laws.

Purpose: Why We Are Using and Sharing Your Protected Health Information

Before explaining the treatment procedure steps, about SNP: SNP is an FDA approved medication used for high blood pressure treatment due to its dilatation effect on vessels. It also affects biological inflammatory markers in the vessel walls. With these mechanisms, SNP might provide better outcomes in Schizophrenic patients via decreased deterioration in brain vascular structures.

SNP in Schizophrenia patients is investigational. This means that the medication is still being tested in research studies and is not approved by the Food and Drug Administration (FDA) for the way that it is being used in this study.

The reason for using and sharing your Protected Health Information is to conduct and oversee the current, secondary, and future research described in this Informed Consent Document. There are many other reasons beyond the research for which BIDMC may use or disclose your Protected Health Information. Not all of these reasons require your express written authorization. For example, we will use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities. The various ways in which BIDMC may use and disclose your protected health information without your authorization are explained in a document called the Notice of Privacy Practices. If you have not received a copy of BIDMC's Notice of Privacy Practices, please ask us for one and review it before signing this form. In addition to signing this document, you may also be asked to sign a BIDMC General Agreement form acknowledging that you have received the BIDMC Notice of Privacy Practices.

No Expiration Date – Right to Withdraw Authorization
Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization to Paulo Lizano at 330 Brookline Ave. Please be aware that the investigators in this study will not be required to destroy or retrieve any of your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter, and they are permitted to continue to use and disclose your previously collected information as necessary to complete the research.

Refusal to Sign
Your clinical treatment may not be conditioned upon whether you sign the Authorization for Research. However, if you choose not to sign this informed consent document and authorization for the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

Right to Access and Copy your PHI

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If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

ADDITIONAL CONTACT FOR QUESTIONS OR CONCERNS
You may contact the Human Subjects Protection Office at [617] 975-8500 in the event that you would like to obtain information or to offer input about the research study. This office is independent of the investigator or investigator's research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH
I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO).

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that BIDMC has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided for in this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____
Signature of Subject Date

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____
SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

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PRINT INVESTIGATOR'S/Co-Investigator's NAME

A signing co-investigator must be listed on the study's approved Research Staffing Form at the time of consent.

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THE FOLLOWING SECTIONS ARE NOT NEEDED FOR ALL STUDIES AND SHOULD BE UTILIZED AS INDICATED:

If the subject is able to speak and understand English but is not able to read or write

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is able to understand English but is not physically able to read or write or see

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is not English speaking and signed the translated Short Form in lieu of the English consent document.

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.
Signature of Interpreter: _____
Printed name of Interpreter: _____
Date: _____