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Version 2.0

DATE:

18 June 2020

REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☐	HHS (Department of Health and Human Services)
☐	VA
☐	Other:

Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

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1. Objectives

Primary Objective

The primary objective of this study is to:

- Assess the safety and tolerability of Isoxsuprine (ISX) in combination with high dose corticosteroids in subjects experiencing acute relapses due to multiple sclerosis.
  The safety analysis population will include all randomized subjects who receive at least one dose of study drug. Safety endpoints will be summarized by treatment group (ISX or placebo) from the time of the first does and include all available safety data. No formal statistical testing will be done. All adverse event data will be listed and will be summarized by treatment group. Quantitative safety variables (vital signs) will be summarized at each visit by treatment group and changes from baseline will be summarized by treatment group at selected visits.

Secondary Objective

The secondary objective of this study is to:

- Evaluate the potential efficacy of Isoxuprine as add-on treatment for improving neurological deficits in walking ability, visual acuity, and other associated symptoms of MS, including fatigue and cognitive dysfunction in this MS population experiencing a relapse.
  The efficacy analyses will include all randomized and dosed subjects who provide Week 12 efficacy data. The key secondary analysis will compare the changes in EDSS functional system scores most relevant to the relapse associated disability (e.g. pyramidal, visual, cerebellar). Also walking speed and z-score from the Multiple Sclerosis Functional composite score (MSFC) from Baseline to Week 12 in the ISX group compared to the placebo group.

2. Background

Overview

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) characterized by multifocal inflammation, demyelination, axonal injury and brain atrophy secondary to neurodegenerative changes. The prevalence of MS in the US is estimated to be 1,000,000 in the US with approximately 2,000 new cases diagnosed annually. MS occurs more often in women than men (2:1 ratio) with a mean age of onset in the US of approximately 33 years. The most common pattern of MS is termed relapsing MS (RMS) where patients experience acute exacerbations or episodes of worsening neurological function followed by partial or complete recovery. Relapses of MS can be associated with transient or permanent disability. For this reason, it is common to treat significant relapse symptoms with short pulses of high dose corticosteroids. Severe relapses involving vision loss, impaired ambulation or other disabling symptoms may recover more quickly with high dose corticosteroids given daily for 3 to 5 days. Evidence from preclinical stroke models

and experimental allergic encephalomyelitis suggest that isoxsuprine hydrochloride may have neuroprotective activity and reduce disability in animal models. Isoxsuprine belongs to the group beta-agonists that cause vasodilation and has been used to treat problems resulting from poor blood circulation and, in certain women, to stop premature labor. Given its potential neuroprotective effects in CNS injury models, we propose to test it as a safe, tolerable add on treatment for acute relapses in patients with relapsing forms of MS.

3. Study Design

Description

This is a proof of concept, randomized, double-blind, placebo-controlled, 2-arm, parallel group study of Isoxsuprine in MS subjects experiencing a typical relapse.

All subjects will have a documented diagnosis of relapsing MS or a clinically isolated syndrome by international criteria. The relapse will be of sufficient severity that their physician recommends treatment with a high dose corticosteroid pulse. All subjects will have a physical examination and history with questions on drug sensitivities. Subjects experiencing the onset of objective neurological deficits consistent with relapse within 7 days of randomization are eligible for screening for this study. Those currently on MS disease modifying therapy will have received a stable regimen of the medications for at least 30 days prior to screening and will continue the same doses and regimens for the duration of their study participation.

Consented subjects will be assessed for relapse criteria and those who meet study eligibility criteria and agree to be treated with a standard 3 to 5 day pulse of high dose corticosteroids, will be randomized with equal probability to 1 of 2 treatment groups: placebo capsule or active Isoxsuprine (ISX).

The Screening Visit will take place within 7 days of relapse onset and within 48 hours of initiating high dose steroids. Subjects may start corticosteroids anytime during this 7 day window. During the screening period, subjects will be assessed with the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and cognitive testing prior to treatment with ISX or placebo (1:1 ratio). Safety Assessments during screening will include a physical exam, electrocardiogram, vital signs, weight and a urine pregnancy test for females of child bearing potential. At 7 (± 1) days following the completion of the 5-day ISX dosing, subjects will be re-assessed with the EDSS.

Subjects will be evaluated for treatment response using the EDSS and other standard measures described below at visits 1, 4 and 12 weeks.

Study drug will be administered as one (1) 10 mg capsule, 3 times daily for 5 days in conjunction with concomitant dosing with high dose corticosteroids. This can be any accepted regimen, including daily iv methylprednisolone 1000 mg/day or 600mg oral

prednisone two times a day at approximately 8AM and noon, with food, as typically provided by UNM MS Specialty Clinic

4. Inclusion and Exclusion Criteria

Inclusion Criteria

Subjects must meet all the following criteria for inclusion in the study at the Screening
Visit:

1. Subjects must be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the ICF;
2. Male or female subjects between 18 and 50 years of age, inclusive;
3. Confirmed diagnosis of Multiple Sclerosis or Clinically Isolated Syndrome (CIS) suggestive of MS, according to the 2010 Revised McDonald criteria.
4. On a stable regimen of medications taken specifically to treat MS for at least 30 days prior to screening, and willing to continue the same doses and regimens for the duration of study participation;
5. New neurological disability consistent with MS relapse no longer than 7 days prior to screening;
6. Screen visit and randomization must occur within 48 hours of subject initiating steroid treatment.
7. Maximum EDSS score during screening of 6.5;
8. Sufficient ambulatory ability (ambulatory aids acceptable if used consistently) to complete two trials of the Timed 25 Foot Walk (T25FW) at the screening visit with the two trials completed within 5 minutes of each other in accordance with the specific instructions provided by the National MS Society Functional Composite Manual.
9. Subject must be willing to take a high dose steroid (600mg oral prednisone two times a day (bid).
10. Subjects must have a mean systolic blood pressure ≤ 160 and greater than 100 mm Hg and a mean diastolic blood pressure of ≤ 100 and greater than 50 mm Hg determined by the average of 3 seated readings taken at least 5 minutes apart at the Screening Visit.
11. Subjects must be able to communicate effectively with study personnel. For this reason only English speaking subjects will be eligible for the study.
12. Subjects must be able and willing to follow all protocol requirements and study restrictions.
13. Subjects must be able and willing to return for all study visits.

Exclusion Criteria

Subjects are ineligible for study participation if they meet any of the following criteria at the Screening Visit:

1. Subject is from a vulnerable population, as defined by the US CFR Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the IRB.
2. Subject has only sensory, bowel/bladder, and/or cognitive symptoms of MS associated with the most recent relapse.
3. Subject has cognitive or behavioral impairment that in the opinion of the investigator would impair the ability of the subject to comply with study procedures.
4. Subject has any known contraindication(s) to the use of corticosteroids or isoxsuprine hydrochloride (ISX), including, but not limited to:
    - any current uncontrolled hypertension, primary adrenocortical insufficiency
    - Any current psychoses, infectious disease, or Cushing's syndrome.
    - Any current congestive heart failure (defined as New York Heart Association (Functional Class III to IV).
    - Peptic ulcer (within 24 weeks prior to the Screening Visit).
    - Recent major surgery (within 24 weeks prior to the Screening Visit).
    - Use of tizanidine any time in the past 30 days.
5. Subject has a clinically significant infection requiring intravenous administration of antibiotics and hospitalization prior to the Screening Visit.
6. Subject has poorly controlled type 1 or type 2 diabetes mellitus (prior diagnosis of gestational diabetes mellitus is not exclusionary
7. Received systemic steroids for a problem unrelated to the MS relapse within 30 days prior to screening.
8. History of other neurological disease that, 'in the opinion of the Investigator, would affect motor function or cognition;
9. For patients with a history of Major Depressive Disorder, at risk for worsening depression due to steroids or the presence of active depressive symptoms sufficient, in the opinion of the investigator, to affect the subject's ability to complete study assessments, or which would not be in the subject's best Interest to participate in the study;
10. Presence of cognitive impairment sufficient, in the opinion of the investigator, to affect the subject's ability to complete study assessments, or which would not be In the subject's best interest to participate in the study;

11. History of sensory impairments (e.g., hearing, vision) that, In the opinion of the investigator, would impair the subject's ability to complete study assessments;
12. History of current alcohol or substance abuse or dependence;
13. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 within 2 years prior to screening, or history of coronary artery disease and/or active angina pectoris;
14. Any clinically significant ECG abnormalities;;
15. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication;
16. If female, is pregnant or lactating;
17. History of hypersensitivity or allergic reaction to any of the study drugs.
18. History of heavy use of tobacco/smoking

5. Number of Subjects

Approximate Number of Subjects

Target enrollment is 20 subjects equally randomized to ISX or matching placebo.

6. Study Timelines

Approximate Duration of Subject Participation

Subjects will participate in the study for a total of up to 12 weeks. Study visits include a screening/randomization visit with drug administered and safety and efficacy assessment visits at weeks 1 (7 days after completion of ISX dosing), 4 and 12 weeks.

7. Study Endpoints

Primary safety endpoints will be assessed using the following:

- Individual GI symptoms
- Adverse events (AEs)
- Vital signs (temperature, respiratory rate, pulse, systolic and diastolic blood pressure)
- Electrocardiogram (ECG) parameters (heart rate, RR, QT, QTcF, QTcB, PR, and QRS intervals)

Secondary efficacy endpoints will be assessed using the following:

- Kurtzke Expanded Disability Status Scale (EDSS0
- Timed 25-foot Walk (25FTW)
- Symbol Digit Modality Test (SDMT)

8. Research Setting

Aside from recruitment which will take place at the Clinical Neuroscience Center, MS Clinic, all research activities will be completed at the MS Specialty Clinic. The MS Specialty Clinic is located at 1101 Yale Blvd, NE, Albuquerque, NM 87131.

9. Prior Approvals

The following approvals are available and will be provided with study documentation:

- Departmental Review Form
- Drug Attachment for Isoxsuprine and matching placebo
- IND Exemption Checklist

10. Study Procedures

Screening Visit (Visit 1) Procedures/Assessments

The following procedures will be performed at the Screening Visit:

- Informed consent.
- Inclusion/exclusion criteria.
- Medical and surgical history.
- Demographics.
- Physical examination.
- EDSS.
- Multiple Sclerosis Functional Composite (MSFC).
- Cognitive Battery consisting of the Symbol Digit Modality test
- Height and Weight.
- Vital signs.
- Urine pregnancy test.
- Electrocardiogram (ECG) pre-dose.
- Treat with oral prednisone (600 mg BID) if not already receiving corticosteroid pulse, which can be via Iv or Po route.
- Adverse events and concomitant medications.

Randomization Visit (Visit 1) Procedures/Assessments

- Initiate treatment with Isoxsuprine HCL (oral) Capsule 10mg or placebo.
- 1 hour monitoring post dose.
- Vital signs.
- Electrocardiogram (ECG) post dose.
- Adverse events.

1 Week Post Treatment Safety Follow-Up Visit (Visit 2) Procedures/Assessments

The following procedures will be performed at this visit:

- Physical examination.
- EDSS.

- Multiple Sclerosis Functional Composite (MSFC).
- Vital signs.
- Adverse events and concomitant medications.

4 Week Post Treatment Safety Follow-Up Visit (Visit 3) Procedures/Assessments
The following procedures will be performed at this visit:

- Physical examination.
- EDSS.
- Multiple Sclerosis Functional Composite (MSFC).
- Cognitive Battery (Symbol Digit Modality).
- Vital signs.
- Adverse events and concomitant medications.

12 Week Post Treatment Safety Follow-Up Visit (Visit 4) Procedures/Assessments
The following procedures will be performed at this visit:

- Physical examination.
- EDSS.
- Multiple Sclerosis Functional Composite (MSFC).
- Cognitive Battery (Symbol Digit Modality).
- Vital signs.
- Adverse events and concomitant medications.

Adverse Events
Adverse events will be recorded from signing of the ICF and followed by the investigator until the AE is resolved or stabilized. Any and all safety measures (which includes standard of care activities) should be provided by the study site to the subject. Any study site follow-up should be documented.

Medical History
Medical history will be obtained at the Screening Visit. Medical history will include a review of the following systems: general medical and surgical history. Historical and current medical conditions including date of last menstrual period for female subjects will be recorded.

Current Medical Conditions
At each visit after screening, subjects will be asked about any changes in medical conditions, specifically new medical conditions and worsening of existing medical conditions. Any changes since the Screening Visit will be recorded as AEs, as appropriate.

Physical Examination
A complete physical examination will be performed at all four study visits. The complete physical examination includes evaluation of the head, eyes, ears, nose, throat, neck

(including thyroid), cardiovascular system, lungs, abdomen, neurological system not obtained with EDSS, skin, extremities and other conditions of note.

The findings of the physical examinations will be recorded. Any change from the Screening Visit physical examination that is considered clinically significant by the investigator will be recorded as an AE.

Electrocardiogram
A 12 lead ECG will be taken at visits baseline and 1 week, (pre and post dose for visit 1).

Height and Weight
Height and Weight will be collected at screening only.

Vital Signs
Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. Additionally, at the Screening/Randomization Visit, blood pressure will be measured at least 3 times, with 5 minutes between assessments after the subject has been seated for a minimum of 5 minutes prior to the initial blood pressure assessment. The date and time for all vital sign assessments will be recorded.

The investigator may perform additional unscheduled vital sign measurements to evaluate or manage a suspected AE. These unscheduled vital sign measurements should be obtained after the subject has been seated for at least 5 minutes, if possible. Unscheduled vital signs will be recorded.

Urine Pregnancy Tests
Urine pregnancy Tests will be completed at visit 1 on females of child bearing potential based on medical history obtained at screening visit.

Symbol Digit Modality Test
SDMT has demonstrated sensitivity in detecting not only the presence of cognition impairment, but also changes in cognitive functioning over time and in response to treatment. The SDMT is brief, easy to administer, and involves a simple substitution task that normal adults can easily perform. SDMT will be administered by a qualified examiner.

11.Withdrawal of Subjects

Subject Withdrawal
Subjects who discontinue, the reason for discontinuation will be recorded. A subject may be discontinued from the study for the following medical or administrative reasons:

- Withdrawal by Subject.
- Adverse Event.
- Death.

- Loss to Follow Up.
- At PI discretion.

Treatment Discontinuation

On rare occasion, oral administration of the drug isoxsuprine has been associated with the occurrence of hypotension, tachycardia, chest pain, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears, the drug will be discontinued. Treatment with study drug should be discontinued if any of the following occur:

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 and diastolic blood pressure ≥ 100 mm Hg) that cannot be managed by the adjustment of concomitant medications such as antihypertensive medications.
- Development of symptomatic hypotension (defined as syncope or orthostatic lightheadedness) or systolic blood pressure ≤100 and diastolic blood pressure ≤ 50 mm Hg).
- Development of congestive heart failure that cannot be managed by the adjustment of concomitant medications such as diuretics and antihypertensive medications.
- Development of diabetic signs/symptoms or classic symptoms of hyperglycemia with random plasma glucose> 200 mg/dL).
- Development of any other AE of at least moderate intensity and possibly, probably or definitely related to study drug that cannot be managed by the adjustment of concomitant medications.

12. Data Management/Confidentiality

Qualified Clinical Trial personnel will be the only ones that will carry out study procedures. MS Clinical Trial personnel will have access to study records. HIPPA Regulations will be strictly followed.

It is required that subjects be explicitly identified by a study number. This number is assigned at screening. A study number link is necessary in case of follow-up for accuracy and/or quality control. The link will be kept at least the duration of the study.

All study data will be entered into a RedCAP data which maintained locally. Only the study id number is used in the database to identify study subjects.

A subject identification log will be kept on-site, however, no copies will be made.

All records will be kept in a locked office at 1101 Yale Blvd NE. Once the study has been closed the data will be stored for up to 3 years per regulations

13.Data and Specimen Banking

Not applicable. We will not be collecting any specimens or banking any data for this study protocol.

14. Risks to Subjects

Along with its needed effects, isoxsuprine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention. Check with your doctor as soon as possible if any of the following side effects occur while taking isoxsuprine:

Rare

- Chest pain
- dizziness or faintness (more common for injection)
- fast heartbeat (more common for injection)
- shortness of breath
- skin rash

Some side effects of isoxsuprine may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

Less Common

- Nausea or vomiting (more common for injection)

Risks to patient confidentiality will be mitigated by good clinical practice procedures as outlined in the protocol. Part of this study is a standard of care treatment for MS relapse and only the addition of isoxsuprine or placebo is the subject of the research.
All patients will be screened and excluded for pregnancy
Careful examination and history will be taken to ascertain key inclusion and exclusion criteria in order to minimize the probability and magnitude of risks.

15. Potential Benefits to Subjects

This is not an efficacy study. The goal here is to study a reasonable number of MS patients in acute relapse who are receiving standard high dose steroid therapy. We will randomize 20 subjects to receive ISX or PBO and assess for any tolerability or safety issues as described in the protocol. Based on this pilot data, it may be reasonable to initiate a larger efficacy study. It is possible that ISX will in fact have neuroprotective properties in MS patients. In that scenario, patients could attain some benefit to their future disability. Again, this is not an endpoint and the study is not powered to detect a clinical benefit.

16. Recruitment Methods

Recruitment

Potential RRMS patients will be recruited and identified from the neurology clinic at the University of New Mexico Hospital. Once identified, the coordinator will contact the potential research patient to discuss the study with them. Once their interest is verified, a copy of the approved IRB consent is sent or given to the patient for their review.

The coordinator will ask the patient to sign a release to obtain copies of their medical records for review. The coordinator will review the medical record prior to scheduling a screening visit. This is done so that if there is anything in the medical records which will exclude the potential research patient, this will be found prior to a screening scheduled visit. This preliminary review of the patient allows them to be deemed eligible to screen for the study.
Subjects must be consented before any study screening tests or assessments are performed. At the time of consent, the subject will be enrolled into the study.
The coordinator and/or study staff will document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the study screening log.

17. Provisions to Protect the Privacy Interests of Subjects

Protections for Subjects

The principal investigator and/or MS Clinical Trial personnel will approach the subject with specific details after they are referred to the clinic or are seen in the MS clinic. Only those study personnel will interact with the patient throughout the study. All information is gathered and stored at 1101 Yale Blvd, NE for Dr. Hainline's review, in case there are any safety issues that need to be addressed.
From the beginning at the ICF process, all study activities are explained in terms the subject can understand and an opportunity is given for the subject to ask questions. This is continued throughout the study. At each visit a lot of time is given to the patient so that they understand the various procedures being done as a safety precaution.
There is a lot of communication and the patient is always encouraged to ask questions either in clinic, at the research facility or via telephone. All of their questions will be answered with a level of compassion, as we understand this is for research.

18. Economic Burden to Subjects

Study Costs

This study will supply the study drug needed for treating the subject's MS relapse while they participate, at no cost to the subject. All of the required study procedures and activities that are above the standard of care will be covered by the UNM CTSC. will pay for all study-required procedures that are above and beyond standard of care. The subject's health insurance company will be billed for the costs of tests that are not covered by the study.

19. Compensation

The subjects will not be compensated for their participation in this study.

20. Compensation for Research-Related Injury

Subject injury

If the subject experiences any unexpected symptoms or injury directly related to the study medication or study procedure which was properly performed in

accordance with this protocol, all reasonable medical treatment will be provided by UNM HSC. Study related injuries do not include injuries that result from subject own fault or intention.

21. Consent Process

Ethical Conduct of the Study

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; FDA regulations including 21 CFR 314.106 and 312.120; and ICH guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Subject Information and Consent

The ICF must be approved by the IRB before any subject provides consent.

At the Screening Visit, subjects will read the ICF and a Health Insurance Portability and Accountability Act (HIPAA) authorization form, after an explanation of the study. Before signing the ICF and the HIPAA authorization form, subjects will have an opportunity to discuss the contents of these forms with study site personnel.

Subjects must assent understanding of and voluntarily sign these forms in compliance with applicable GCP guidelines and 21 CFR, Parts 50 and 312 (where applicable), before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures and written informed consent must be obtained from a legally authorized representative in accordance with national and local laws.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations including confidentiality. All versions of each subject's signed ICF will be kept on file by the site for possible inspection by regulatory authorities. Signed copies of the ICF and the HIPAA authorization form, if applicable, will be given to the subject.

If the subject withdraws consent and/or HIPAA authorization, the investigator will no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

- ***Partial Waiver of HIPAA Authorization*** *This study will seek a* ***partial waiver of HIPAA authorization*** *in order to review the medical records of current MS patients for screening procedures.*

22. Documentation of Consent

Consenting Process

The Principal Investigator or authorized representative reviews the ICF by discussing and or explaining study procedures, treatments, costs, potential benefits/risks involved, and the alternatives for care or treatment to the patient. The person obtaining consent is knowledgeable about the protocol and able to answer any questions. All study procedures are explained in terms the subject can understand and an opportunity is given for the subject to ask questions. The PI or authorized representative ensures the subject meets inclusion exclusion criteria. Expectations of subjects are reviewed. Special care is given to explaining the use and disclosure of the subject's protected health information. This is done before the informed consent is signed. The investigator documents this discussion in the patient's chart.

After the PI has explained the trial and determined the subject's interest level, the designated research staff or "person obtaining consent" will verify the subjects understanding of the study, ensuring the subject has adequate information in making the decision to participate in the clinical trial. After all questions are answered, both subject and PI or authorized representative sign ICF.

A copy of the fully executed and signed ICF is provided to the subject for their records. The original ICF will be kept in the subject's study biner.

The full ICF process is completed prior to any study assessments and is documented in site's requisition form.

23. Study Test Results/Incidental Findings

Some diagnostic testing information will be given to the patient to include: Vitals, weight, Physical Exam. The patient will be given the information directly for them to share with their PCP.

24. Sharing Study Progress or Results with Subjects

Due to the length and the blinded nature of the study, there is no plans to share study progress or results with the study subjects at this time.

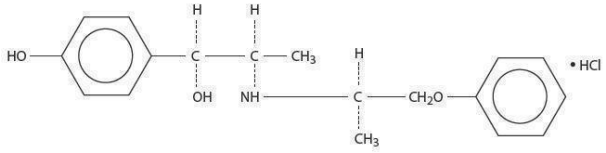
25. Inclusion of Vulnerable Populations

N/A This study does not seek to recruit participants from vulnerable populations.

26. Drugs or Devices

Product Description

Isoxsuprine hydrochloride (ISX)



Isoxsuprine hydrochloride structure

Formulation and dosing: Compounded capsules with identical placebo, 10 mg by mouth 3 times per day for 5 days

Methods of Assigning Subjects to Treatment Groups
Subjects will be randomized 1:1 according to a computer-generated allocation scheme to receive either Isoxsuprine HCL 1 capsule 3 times daily for 5 days or matching placebo.

Emergency Identification of Investigational Medicinal Product
In case of an emergency during the study, when knowledge of the investigational product assignment is required for the medical management of an individual subject experiencing the emergency, the treatment blind for that subject may be broken by contacting the research pharmacy. The investigator must also indicate in source documents that the blind was broken and provide the date, time, and reason for breaking the blind.

Dosing Procedures
The medication should be kept at room temperature and will be labeled according to all applicable national and local regulations.

The following treatments will be administered:

- Treatment A: Isoxsuprine HCL 1 Capsule 3 times daily for 5 consecutive days, OR
- Treatment B: Placebo 1 Capsule 3 times daily for 5 consecutive days.

The subject or clinic staff will administer the first dose of drug in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour post-dose to monitor for allergic or adverse reactions. Thereafter, all doses will be administered by the subject or the subject's caregiver at home.

Subject Unblinding
The identity of the treatment assigned to individual subjects can be revealed in an emergency only. A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the safety of the subject

Storage of Clinical Supplies
Isoxsuprine HCL and placebo will be maintained in a temperature controlled, secure locked area with restricted access at the study site pharmacy.

Drug Accountability
Subjects will be asked to return all empty study medication containers at study visit week 1 (Visit 2). They will be asked if all study medication was taken as directed.

Safety Assessments and Procedures
The following safety assessments will be evaluated (see section 10): AEs, physical examinations, ECGs, vitals, weight, urine pregnancy tests and Concomitant Medications.

Michel Torbey, MD and Mark Unruh, MD to serve as a Data Safety Monitoring Board. They will have no connection to the study. On a quarterly basis, study progress and data will be submitted for review. Adverse events will be reported to the DSMB and IRB within 7 days and Serious Adverse Events within 24 hours. The DSMB will help ensure patients safety and rights though out the study. The DSMB will have authority to provide recommendations on the conduct of the study, such as suspension of the study or advise on any potential protocol revisions.

IND Waiver Justification

This study proposes to use isoxsuprine HCl (ISX) in standard 10 mg tablets in subjects experiencing an acute relapse of multiple sclerosis. The rationale comes from strong preclinical observations that ISX had significant and novel neuroprotective action in ischemic stroke using a cell-based high-throughput screening (PLOS ONE, 1 May 2014, Volume 9 (5) e9676.). Isoxsuprine was identified as a top neuroprotectant among 1,200 compounds in the Prestwick Chemical Library, which contains diverse, mostly FDA-approved and off-patent compounds, and its neuroprotective function was confirmed in transient ischemic injury in animals. ISX has been used in the past for suppressing premature labor and for vascular dementia, since the drug is a beta-adrenergic agonist and vasodilator. These older indications are not used very often now but a typical dose was 10mg by mouth 3 to 4 times per day. In this tolerability and safety study we will use 10mg tid as the dose, given for 5 consecutive days. The primary goal is to assess safety and tolerability in MS patients in a relapse, who are also receiving a short course of high dose steroids to shorten relapse recovery. These subjects are otherwise healthy and will not have significant other health issues. We do not anticipate adverse reactions to concomitant use of ISX and steroids. While ISX tends to lower blood pressure modestly, steroids tend to increase, essentially in offsetting directions. Subjects will be randomized to ISX 10mg tid x 5 days or matching placebo. They will initiate the ISX within 48 hours of starting steroids.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

1. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☒ Yes. Describe: *Only information found from potentially eligible subjects will be recorded. Information such as name, DOB, medical data, including laboratory test results, radiology and pathology results, information about other medical conditions that may affect their participatio*n.

   ☐ No

2. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

   This information will only be collected for potentially eligible participants. Subject will be consented and those found eligible will be and this information will become part of their study source documentation. Subjects found to be ineligible will have their reason for exclusion documented and this information will become part of their study source documentation. Those patients who do not sign consent will have their PHI destroyed upon their decline to participate.

3. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☒ True

   ☐ False