A pilot, proof of concept, placebo-controlled, parallel study of the effects of high dose intranasal oxytocin for the treatment of tinnitus

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Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
1.0	14 JAN 2020	Original version
1.1	6 MAR 2020	Modified Visit 2 (Baseline Visit) to be a phone visit instead of an office study visit.
1.2	7 JUL 2020	Changed compounding pharmacy to New Drug Loft/VLS Pharmacy due to issues with Town TOTAL Compounding Pharmacy's quality control. Accordingly, the placebo formula has been modified to include the same inactive ingredients as the oxytocin nasal spray to mirror the consistency of the active drug. The new Headache Fellow has been added to the IRB application.
1.3	31 DEC 2020	Modified the time period subjects receive the minimum dose of 30 IU oxytocin from 3 weeks to 2 weeks to allow subjects to reach the maximum dose of 45 IU before randomization occurs, since study drug is dispensed every 2 weeks. Also, per the Conflict of Interest Management Unit, the physician overseeing the Data Safety Monitoring of the study has been

		changed from Dr. Thomas Berk to Dr. Scott Grossman, a disinterested third party.
1.4	6 APR 2021	Modified to include the potential risk of acute pulmonary edema after one participant experienced this unanticipated event while using the compounded oxytocin nasal spray. Exclusion criteria revised to include history of pulmonary edema, CHF, and severe renal disease.
1.5	17 MAY 2021	Modified to increase the number of participants screened to 50, with the same goal of enrolling 30 participants in the study. This number has been modified to account for the larger number of participants who failed screening due to abnormal results, as well as the participants who were enrolled and withdrew due to noncompliance, adverse events, or hesitance to travel during the pandemic.
1.6	6 JUL 2021	Modified to replace the previous Headache Fellow and Sub-Investigator, Dr. Huang, with the new fellow, Dr. Thaler. Dr. Huang completed his fellowship and is no longer at this site. Dr. Thaler has been trained on the randomization procedures for this study.
1.7	16 NOV 2021	Modified to add Dr. Tamimi, another new Headache Fellow, to the study team. He has also been trained on the randomization procedures for the study. Also, Section 5.7.2, Handling of Participant Withdrawals or Termination, has been modified to state that we plan to replace participants who withdraw or discontinue the study early. This is being changed to allow for the necessary data collection outlined in Section 9.3, Analysis Datasets, of the Statistical Considerations; data will be analyzed from participants who receive at least one dose of the study drug during the non-blinded phase, and also pass the 2-week washout period in the double-blind phase. In order to capture this data to determine efficacy of the drug, 30 participants must complete all visits through Week 12 of the study (Visit 14). This can only be done if we replace the participants who withdraw or discontinue the study early. The number of participants screened will remain unchanged since Version 1.5 of the protocol, at 50.

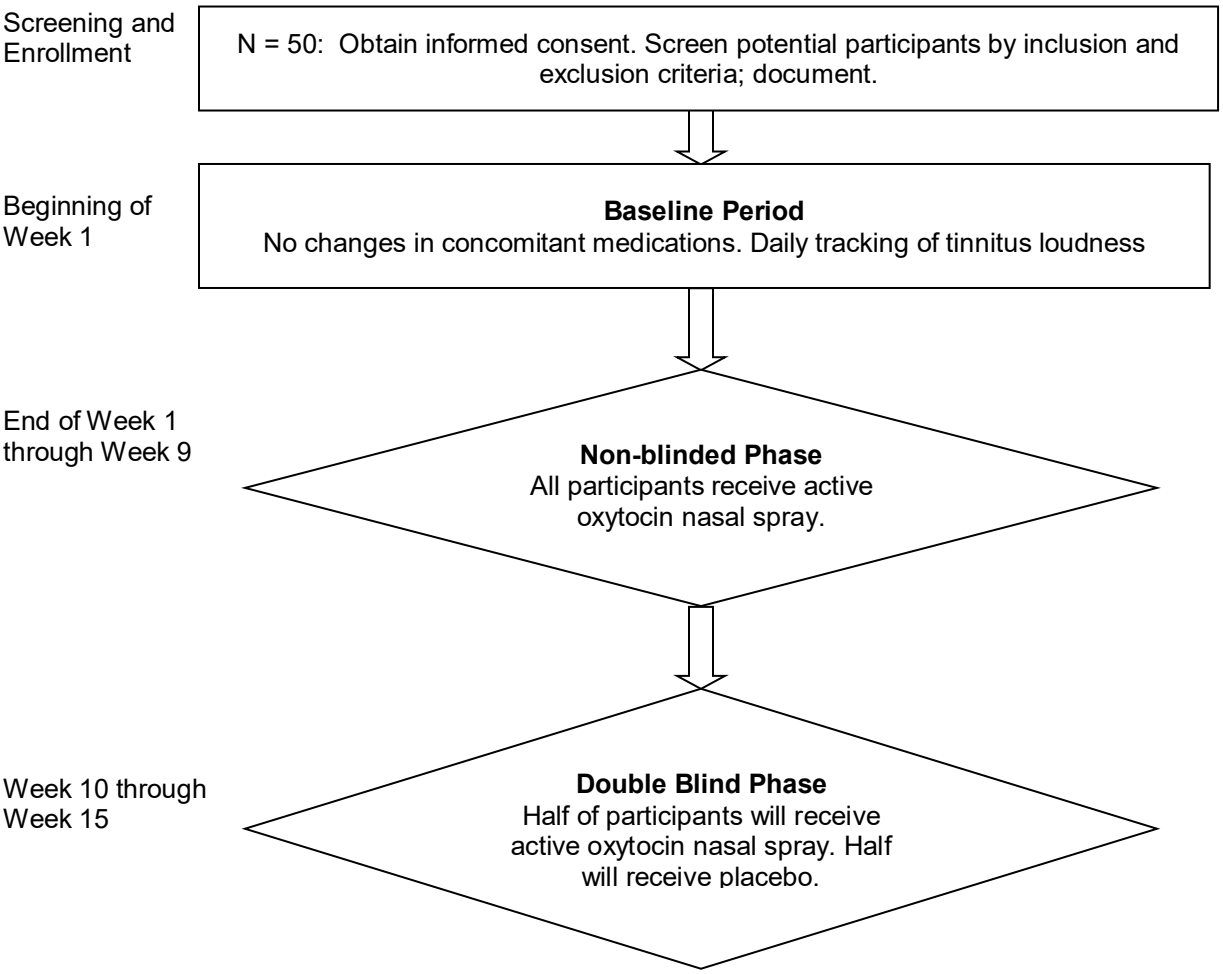
Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Protocol Summary

Title	A pilot, proof of concept, placebo-controlled, parallel study of the effects of high dose intranasal oxytocin for the treatment of tinnitus
Short Title	High Dose Oxytocin Nasal Spray for Treatment of Tinnitus
Brief Summary	The purpose of this study is to evaluate the effects of high-dose intranasal oxytocin for treating tinnitus. The hypothesis is that high dose intranasal oxytocin can significantly reduce tinnitus severity and disability.
Methodology	Pilot, proof of concept, randomized, placebo-control, parallel study
Endpoint	The primary efficacy endpoint is the area under the VAS curve from baseline for all randomized participants during the blinded study phase. The secondary endpoint, which is exploratory, will be improvement ($p < 0.10$) in the Tinnitus Handicap Inventory Severity Scale (THI)/Clinical Global Impression Scale (CGI) and Tinnitus Functional Index (TFI).
Study Duration	Time from when the study opens to enrollment until completion of data analysis will be approximately 1 year.
Participant Duration	Participant participation will last approximately 4 months and involve about 17 visits.
Duration of IP administration	Investigational product administration will last 15 weeks. The first 9 weeks of this period will involve the administration of active study medication to all participants. During the last 6 weeks, participants will be randomized to receive either placebo or active study medication for the remainder of the study.
Population	We will recruit patients from NYU Langone Medical Center's Departments of Otolaryngology and Neurology. Eligible individuals will be age 18 to 75 with continuous perception of tinnitus for > 6 months, with a normal ENT evaluation within the past year.
Study Sites	NYU Langone Medical Center
Number of participants	50 participants expected to be enrolled with a goal of 30 study participants remaining after accounting for screen failures and participants who withdrew from the study.
Description of Study Agent/Procedure	The investigational product, oxytocin nasal spray (45 units/0.1mL for 100mL) is composed of: oxytocin 10 unit/MG/mannitol trituration (4.500g), magnesium chloride crystals (6.080g), citric acid anhydrous gran. (0.284g), sodium citrate powder (5.660g), sterile water for irrigation (100.000mL), and Pcca Mucolox liquid base (10.000mL). The dose for the oxytocin nasal spray will range from 30 to 45 IU per puff to be administered four times per day, for an equivalent to 120 to 180 IU oxytocin/day.
Reference Therapy	The investigational product will be compared to placebo, a nasal spray consisting of magnesium, chloride crystals, citric acid anhydrous gran., sodium citrate powder, sterile water for irrigation, and Pcca Mucolox liquid base.
Key Procedures	Oxytocin (or placebo) will be self – administered by the study participants daily. Study visits will occur every two weeks, from prior to the baseline week to 15 weeks after baseline, during which patients will be asked to rate the loudness of their tinnitus (VAS scale) and complete the THI questionnaire. Additional questionnaires and urinalysis will be performed at every study visit to monitor sodium levels and osmolality.
Statistical Analysis	The primary analysis is to provide an estimate of the partial eta squared effect size difference between placebo and treatment during the blinded phase of the study as well as to provide initial efficacy, safety and tolerability estimates during the initial open label study phase.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Tinnitus, the perception of noise in the absence of an external stimulus, is a common, disabling and poorly understood phenomenon. Population based studies estimate the prevalence of tinnitus in the United States to range from 8-23%; in other countries, rates of 5-30% have been reported. In a recent study of adults experiencing tinnitus in the preceding 12 months, it was estimated that 1 in 10 Americans are affected. Fifty-six percent had lived with tinnitus for at least 5 years and 27% had symptoms for more than 15 years. Strikingly, 35% of respondents had nearly continuous tinnitus. More than 7% reported that they considered their tinnitus to be a big or very big problem; which would suggest that 15 million Americans are significantly affected (1). Chronic tinnitus affects approximately 50 million Americans and yet there is currently no FDA-approved first-line treatment for the condition.

Tinnitus is generally divided into two categories: objective and subjective. Objective tinnitus is defined as tinnitus that is audible to another person, often as a result of turbulent blood flow, or muscle or palatal contractions, whereas subjective tinnitus, the most common subtype, is perceived only by the patient and usually occurs in the absence of an acoustic etiology (2).

Originally believed to be an otolaryngologic disorder, recent studies suggest that, in fact, tinnitus is most likely a neurological disorder. Tinnitus is often the result of alterations within parts of the auditory pathways. This pathway encompasses the cochlea in the periphery transiting to the midbrain and terminating in the auditory cortex. Damage to the cochlea produces alterations in neuronal activity in which both cortical and subcortical projections adjust to the lack of output with ensuing changes in neural plasticity. These changes in neuroplasticity result in neuronal hyperactivity at various sites in the auditory pathway (dorsal cochlear nucleus, inferior colliculus, auditory cortex, and the striatum) and ultimately reorganization of the auditory tonotopic map (3).

Outside of the auditory pathways, changes are also noted in the limbic system in patients with chronic tinnitus. These changes are not surprising as there are numerous reports attesting to the emotional and affective comorbidities of tinnitus (4). Imaging studies reveal increased activation in the auditory cortex and amygdala in patients with tinnitus and psychological distress (5).

Oxytocin, a 9-amino-acid neuropeptide, is produced by the magnocellular neurons of the hypothalamus, stored in the posterior pituitary and released into the bloodstream from the posterior lobe of the pituitary gland. Oxytocin plays a role in parturition and lactation, sperm transport and ejaculation, and has been shown to promote social bonding and other pro-social interactions. It is also believed that oxytocin may modulate human fear and anxiety responses (6).

Parenteral administration of oxytocin has long been used for the initiation of labor as well as to control postpartum bleeding. Parenteral oxytocin must be administered in hospital settings with careful monitoring. As oxytocin is structurally and functionally related to vasopressin, it can have a direct antidiuretic properties. Oxytocin has direct renal antidiuretic action by binding to vasopressin and oxytocin receptors in the kidney. When infused at high doses (> 20mU/min), there is a potential for oxytocin cross-reactivity with vasopressin which could result in water retention and a dilutional hyponatremia. This risk is increased when oxytocin is intravenously administered with D5W or when high dose infusion protocols are used (7). Acute pulmonary edema following the use of oxytocin during cesarean section together with other oxytocic drugs has been reported as a rare complication of treatment. (8, 9, 10). Additionally, aqueous oxytocin is heat sensitive and therefore requires refrigeration to maintain potency. To combat this drawback, Milewski et al. studied the stability and absorption of an intranasal dry-powder formulation of oxytocin that did not require refrigeration (11). In this animal study, using cynomolgus monkeys, that have a similar nasal morphology as humans, the authors found that the intranasal route of administration had an approximately 12% relative bioavailability compared with intramuscular dosing.
Intranasal application of oxytocin offers clinicians and patients a noninvasive alternative. The nasal cavity allows for the oxytocin to gain access to the brain by crossing the blood brain barrier in small yet biologically relevant amounts (12). Intranasal administration has been shown to raise CSF and serum levels of oxytocin in animal and human studies (13).

Intranasal administration of oxytocin has also been shown to reduce fear through its action on the amygdala, and could therefore play a role in its lessening the distress caused by tinnitus (14). Predicated upon the above findings of the pathophysiologic underpinnings of tinnitus, the potential interactions of oxytocin on some of these brain regions and a recent publication by Marlin et al documenting the ability of oxytocin to modulate the inhibitory function of the auditory cortex, Azevedo et al conducted a pilot study to evaluate the effect of low-dose oxytocin on tinnitus intensity and distress in patients who had subjective, continuous tinnitus of at least 6 months duration (5, 15). They found that daily use of 16 IU of oxytocin reduced tinnitus-related handicap (THI) scores and to some extent, improved tinnitus distress. These investigators, in this pilot study, or others to our knowledge, have never increased the daily dose above 16 IU.

Based on their findings, I employed a similar strategy to treat two patients with tinnitus in the NYU Langone Medical Center Department of Neurology. In both patients, I initially instituted treatment as per the Azevedo et al trial, with 16 IU of oxytocin daily (1 spray containing 4 IU oxytocin in each nostril twice daily). Both patients noted tinnitus loudness was mitigated after a spray, and that after approximately 2 weeks, the tinnitus intensity was reduced. Based on these reports, and while monitoring serum electrolytes, the dose of oxytocin was gradually increased every 4 weeks. I had oxytocin nasal spray compounded so that each spray was equal to 15 IU. At a dose of 30 IU (1 spray in each nostril) BID both patients reported a significant reduction in tinnitus intensity. At this dose, Patient 1 reported that his tinnitus lessened but gradually built in intensity until his next dose later that evening.
Based on the partial benefit experienced by the patients, I hypothesized that the dosing paradigm was inadequate and increasing the dose and/or frequency of dosing could increase the duration of symptom improvement. This hypothesis is supported in the literature.

Because the very short plasma half-life of nasally administered oxytocin (3-17 minutes), it was possible that the twice daily dosing employed by Azevedo et al. was insufficient to produce a sustained and meaningful relief of tinnitus (16). Reviewing the literature, I found that most studies that employed oxytocin nasal spray used once or twice daily dosing at low doses, because that was what had been utilized in past studies

without producing serious adverse events. Nearly every study concluded that studies employing higher doses should be attempted in the future.

MacDonald et al. reviewed the safety and side effects of intranasal oxytocin in human studies (17). They reviewed 38 randomized controlled trials conducted over a 20 year period, involving 1529 subjects. These studies used doses from 18-40 IU in doses ranging from once daily to 4 times daily. Most of the participants in the studies (76%) were healthy adults 20-30 years old. Of the 1529 study participants, 926 received oxytocin. Importantly, of the 1529 participants, mild side effects were reported by 18%. The main categories of side-effects included: feeling more calm, relaxed or comfortable, or having more energy (5%), drowsiness, lightheadedness or headaches (6%), and nasal irritation, dryness of the mouth or throat (3%). Importantly, there was a nearly 1:1 relationship between the frequency of side-effects reported in the active and placebo arms. A Wilcoxon signed rank test found no significant difference between the frequency of side-effects reported for oxytocin or placebo.

Although the majority of the studies employed low dose or single doses of oxytocin nasal spray, 2 studies employed 40 IU QID for one week, and 1 study used 40 IU BID over 13 weeks. That long term, double-blind, placebo-controlled trial studied the effects of high-dose oxytocin nasal spray in 59 women with chronic constipation (18). Twenty-nine women received oxytocin; the authors reported no changes in blood pressure or electrolyte concentrations in either study arm. Five woman reported menstrual irregularities (1 with oxytocin, 4 receiving placebo). Eleven in the oxytocin group and 12 subjects in the placebo group reported mild side-effects consisting of headache, nausea, abdominal pain, weight gain and nasal irritation. The authors found no significant differences between treatment with oxytocin or placebo, and concluded, “the short half-time of oxytocin, in combination with only two administrations daily, might explain the absence of effects on constipation in our study.”

Many of the studies of intranasal oxytocin as treatment for a variety of psychiatric disorders in humans were underpowered (19). Clinical trials of oxytocin nasal spray have employed dosages ranging from 15 IU to more than 7000 IU (20). Den Boer and Westenberg, in a double-blinded, placebo-controlled study of 12 patients with obsessive-compulsive disorder (OCD), employed 40 IU oxytocin QID for 6 weeks. There were no changes in blood pressure or weights; in the placebo group, one patient complained of headache and in the oxytocin group, four patients had mild dizziness, and two patients reported dry mouth and mild headache. Additionally, they reported in this paper that they gave 2 patients a threefold higher dose, without producing side-effects. High doses of intranasal oxytocin were assessed in 7 patients with OCD; 5 received 160 IU daily and 2 with 320 IU daily. The authors reported there were no significant changes in blood pressure, pulse, or serum osmolality and “side effects were minimal” but not detailed (21). Although this study employed much higher doses than were previously studied in OCD, the treatment phase only lasted one week and failed to show any significant differences between the active and placebo arms. Here too the authors noted that the failure to obtain therapeutic efficacy may have been due to the short period of drug administration and that “even at high doses, a week of intranasal oxytocin administration does not sufficiently effect the CNS to result in a change in behavior.”

Four case reports (5 patients) of adverse reactions to oxytocin nasal spray were identified through an on-line literature search. One was of a 55 year old man with OCD treated with daily doses of oxytocin 8.4-16.8 IU administered 3 times daily over 4 weeks who developed psychotic symptoms and memory loss associated with low plasma sodium and osmolality (22). Two patients using intranasal oxytocin to facilitate lactation developed severe water intoxication; both patients were using “excessive self-administrations” of oxytocin, one was receiving large amounts of intravenous fluid during an in-patient admission for a viral illness, the other was drinking 5 liters of herbal tea daily (23). Two patients given oxytocin intranasally 40 IU QID for a week and saline placebo for a week to treat trichotillomania had no significant changes in blood pressure and pulse measurements. One patient reported one day of increased anxiety, and the other slight nasal irritation, both while taking placebo (24).

While there is no evidence in the literature of the intranasal formulation of oxytocin specifically causing pulmonary edema, one of the participants enrolled into our study, has experienced this adverse event on

the 40 IU four times daily dose. After 11 days at this dose, he noticed shortness of breath and decreased exercise tolerance. His chest x-ray and subsequent CT was consistent with mild pulmonary edema.

Although no longer available in the United States, intranasal oxytocin is marketed in several European countries to improve lactation. Product information from the Netherlands noted that headaches, nausea and allergic dermatitis occurs rarely (>1/10,000, <1/1000), and abnormal uterine contractions may occur at times (≥1/100, <1/100) (17). As detailed in the report of Hubner-Mayer, prolonged use of excessive doses ***together*** with large volumes of fluid has been linked to water intoxication with hyponatremia. The patients reported were self-medicating at doses significantly higher than will be employed in our study. This rare adverse reaction of water intoxication with oxytocin usage is probably the result of similarities between oxytocin and vasopressin, which acts as an anti-diuretic.

In reviewing the published reports employing oxytocin nasal spray as treatment for a variety of medical and psychiatric conditions, which includes several hundred subjects, there have been no reports besides the ones mentioned above, who have developed pulmonary edema. Additionally, we have treated 14 patients in our study without this adverse event, and 3 of my patients have received high dose intranasal oxytocin for 2 years, without evidence of laboratory abnormalities, or complaints of shortness of breath.
For the above reasons, I believe that the risk of pulmonary edema (our case would be the only reported who did not have co-existent fluid overload that was either self-inflicted or occurred with iatrogenic intravenous fluids overload) is exceedingly low and therefore does not increase risk or decrease the acceptability of the risk, and should allow for a continuation of an IND Exemption.

Since the literature supported the relative safety of using higher doses, I decided to change the dosing in both of my patients, while monitoring serum electrolytes.

In patient 1, increasing the frequency to 30 IU (2 sprays in each nostril) TID reduced the intensity of the tinnitus for longer periods of time, but the intensity continued to increase before the next dosing period. Ultimately, increasing the dosing to 45 IU (3 sprays) TID and then QID produced a dramatic and sustained improvement. His THI was reduced from 96 (catastrophic) to 16 (mild or no handicap); his tinnitus loudness decreased from 9-10/10 to 3-4/10, but more importantly, at the higher dose, his 2 year constant, unremitting tinnitus improved so that the perception of noise is present on only 6 or 7 days per month. He has no tinnitus on the other days. Unfortunately, the patient complained that his nostrils would drip for up to 30 minutes after each dose, which was not only embarrassing but made it difficult to ascertain if the entire dosage was being administered and absorbed. To simplify the dosing regimen, I had the spray reformulated so that each spray contained 45 IU and had a non-drip additive, Pcca Mucolox, added to the bottle. On 3 occasions, he was unaware that his medication was improperly stored, and each time, tinnitus recurred within 24 hours.

Patient 2's scores were reduced to a significant but lesser extent because the patient is unable to dose 4 times daily as instructed. Nonetheless, at 45 IU BID his THI decreased from 75 (severe handicap) to 18 (mild handicap) and tinnitus loudness decreased from 7/10 to 4/10 but remains constant. Neither patient experienced significant adverse effects or changes in their vital signs or serum sodium levels. Patient 2 occasionally reports burning in his nostrils.

We postulate that long term treatment with high-dose oxytocin may reduce the frequency and severity of tinnitus, the burden tinnitus symptoms cause patients, and improve their quality of life. However, since the 2 patients were treated with oxytocin compounded as 15 IU per spray, and doses were increased by 15 IU, I cannot be certain that a dose between 30 IU QID, the dose at which both patients initially reported improvement, and 45 IU QID, the dose that produced significant improvement, may have produced similar benefit.

The study will be conducted in compliance with the requirements for institutional review set forth in part 56 and within the requirements for informed consent set forth in part 50, and the investigation will be conducted in compliance with the requirements of 312.7.

2.2 Name and Description of the Investigational Agent

The investigational product is an oxytocin nasal spray composed of: oxytocin/MG/mannitol trituration, magnesium chloride crystals, citric acid anhydrous gran., sodium citrate powder, sterile water for irrigation, and Pcca Mucolox liquid base.

The placebo nasal spray consists of magnesium chloride crystals, citric acid anhydrous gran., sodium citrate powder, sterile water for irrigation, and Pcca Mucolox liquid base. Both placebo and active drug will be handled and stored the same way, in amber glass bottles and kept between 36°F to 46°F (2°C - 8°C).

We believe this study meets the criteria for IND Exemption for the following reasons:
Oxytocin has been tested and is approved by the FDA in different indications. This will be a proof of concept study only, and therefore it is not intended to be reported to the FDA in support of a new indication. If this pilot study, proof of concept study, is successful, we plan to initiate a large-scale study that would then be used to support a new indication, requiring IND application.

We do not intend to use the results of this study to support any change in the advertising of this product and are not affiliated with any sponsors that carry vested interest in the commercial presentations of oxytocin.

2.2.1.1 Clinical Data to Date

See background data in Section 2.1.

2.2.1.2 Dose Rationale (if applicable)

Although the route of administration (nasal spray) used in this study differs from the currently parenteral administration, nasal spray applications of oxytocin have been previously employed for a number of different medical and psychiatric conditions as well as in healthy controls for more than a decade. A recent meta-analysis detailed these studies in which doses of oxytocin ranged from 15 to more than 7000 IU were given without significant adverse events (20). Additionally, recommendations for the standardization of oxytocin nasal administration and guidelines for its reporting were published in the past decade (25). The authors stated “Transmucosal nasal delivery provides a non-invasive alternative route for drugs with poor systemic bioavailability after oral administration. Intranasal administration causes minimal discomfort for the patient, is simple to use, and typically results in high compliance.”

Although this study will use a dosage of oxytocin that is higher than used in a previous study of tinnitus (45 IU QID vs 8 IU BID), it is well within the dose range reported in other studies in the psychiatric literature. In those studies, adverse events were rare, non-life threatening and fully reversible.

Additionally, oxytocin nasal spray has been reported in other studies to be very safe (17).

We therefore believe that neither the route of administration nor dose employed in this study would significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug product.

2.3 Rationale

The hypothesis is that high dose intranasal oxytocin can significantly reduce tinnitus severity and disability. We hypothesize that treatment with high dose oxytocin nasal spray will result in a significant improvement of tinnitus loudness as measured by VAS when compared to placebo.

Relatively high rates of placebo response have been seen in several studies of tinnitus. As in other subjective symptoms, such as pain and affect, short term improvement after placebo can be meaningful. Therefore, the need of run in phase to determine the true response rate to the active intervention.

2.4 Potential Risks & Benefits

2.4.1.1 Known Potential Risks

Greater than minimal risk. Due to the risk of uterine contractions associated with oxytocin use, female subjects of childbearing potential will be instructed to use a double barrier of birth control and the PI will discuss with them the potential dangers if they were to become pregnant while using the drug. It is possible that high dose oxytocin may cause recruitment of vasopressin leading to a decrease in plasma and an increase in urine osmolality and a decrease in serum sodium levels. As a result, there is the less common risk of developing acute pulmonary edema. The main categories of side-effects include: feeling more calm, relaxed or comfortable, or having more energy (5%), drowsiness, lightheadedness or headaches (6%), and nasal irritation, dryness of the mouth or throat (3%). Patients with any serious adverse events will be immediately withdrawn from the study. However, because of the extremely short half-life of oxytocin, any adverse event would not be expected to be long-lasting.

There is the possibility of bruising from the needle site after blood draws at scheduled visits.

Subjects will be monitored with regular communication to note study challenges or adverse events. Individuals will work with study personnel who have been appropriately trained and access to data will be limited to an as needed basis. Information linking the linkage codes to participant's names, medical record numbers, and social security numbers will be stored in a secure location separate from the medical information and only accessible to members of the study team when needed, after approval by the NYU School of Medicine IRB and Principal Investigator. This access will be documented.

2.4.1.2 Known Potential Benefits

Subjects may or may not directly benefit from being in the study. Close medical monitoring of their symptoms may be a potential benefit if subjects are seen infrequently otherwise. Furthermore, if the medication is effective for tinnitus, participants may indeed improve. However, the overall benefit of participating in this research is that it may help others with tinnitus in the future.

3 Objectives and Purpose

The purpose of this study is to evaluate the effects of high-dose intranasal oxytocin for treating tinnitus.

The primary outcome measurement will be a change in the VAS at 3 timepoints:
1. Comparative endpoint of VAS of all 30 subjects at 9th week of treatment with active drug vs baseline.
2. Comparative endpoint during the cross-over phase of VAS at the 17th visit (15th week of study) between the 15 subjects who received placebo vs the 9th week of the non-blinded phase for the same subjects (when they were on active drug). This endpoint compares the 15 patients that were switched from active to placebo and compares their response on placebo (from the double blind phase) with their response on active drug (from the non-blinded phase) and compares them to the 15 subjects that remained on active drug during the entire study.
3. A parallel group analysis where we compare both arms in the last week of the double-blind phase—so in essence we are comparing those 15 who were on active throughout the entire study to those that started on active and changed over to placebo.

Secondary endpoints of interest are also defined a-priori:
1. A change in the THI by at least one grade contrasting the 9^{th} week (end of the single blinded phase) and the 15^{th} week of the study (end of the double blinded phase) between the 15 subjects who were switched from active drug to placebo.
2. A change in the THI by at least one grade during the last 2 weeks of the double-blind stage (weeks 14 and 15 of the study contrasting those on active drug vs. placebo.

Exploratory endpoints of interest include:
Clinical Global Impression (CGI) measured following the same approach of the primary endpoints.
Tinnitus Functional Index (TFI) measured following the same approach of the primary endpoints.

3.1 Primary Objective

To significantly improve tinnitus loudness as measured by VAS, when using intranasal oxytocin compared to placebo.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a pilot, proof of concept, placebo-controlled, parallel study. Participants will be recruited from NYU Langone Medical Center's ENT Department and will receive either high-dose intranasal oxytocin or the placebo, a nasal spray containing the same inactive ingredients as the active drug: magnesium chloride crystals, citric acid anhydrous gran., sodium citrate powder, sterile water for irrigation, and Pcca Mucolox liquid base to replicate the feel and consistency of the oxytocin nasal spray. When changing the compounding pharmacy, we conducted a blinded test of placebo formulations. We found that the placebo containing all of the inactive ingredients as the active oxytocin nasal spray was a significantly better match in consistency to the active drug, as compared to distilled water and Pcca Mucolox. The primary outcome measure for this study will be a greater than 50% improvement in tinnitus loudness on the Visual Analog Scale (VAS). The secondary outcome measure will be improvement ($p < 0.10$) in the Tinnitus Handicap Inventory Severity Scale (THI)/Clinical Global Impression Scale (CGI) and Tinnitus Functional Index (TFI) (26, 27, 28). The metrics on the secondary endpoints are exploratory only and as such we will not look for specific changes. These results will guide us in the next, larger study.

The study will consist of 3 phases:

1. A 1 week baseline phase during which time we will track daily tinnitus loudness on VAS using a study log. Patients will not receive any study drug during this phase. No changes in any concomitant medications will be allowed during this phase. In addition, the use of dinoprostone or ephedrine is not permitted throughout the study.
2. A 9 week non-blinded phase is which all patients will receive the oxytocin nasal spray 4 times daily. All patients will begin at a dose of 30 IU 4 times daily for 2 weeks; If no response is reported (defined as a decrease in VAS of < 2), they will have the dose increase by 5 IU per spray every 2 weeks, until a maximum dose of 45 IU 4 times daily. If patients report improvement (defined as improvement in VAS >3) at any dose, they will remain at that dose through the end of the second phase. In the event that the patient experiences a moderate side effect, the dose will be decreased to the previous dose for the remainder of this phase.
3. A 6 week double-blinded phase in which half of the participants will receive oxytocin nasal spray and half will receive placebo nasal spray. Neither the PI nor subject will know which drug they are receiving. However, the study coordinator will have access to this information as required to assign the medications.

Patients will come to the Preston Robert Tisch Center for Men's Health for study visits every 2 weeks and be administered the VAS and THI/CGI scales by the research coordinator or principal investigator. The screening visit will be the most comprehensive and include obtaining informed consent, a physical exam with vital signs, laboratory studies, questionnaires, an ECG, and review of medical and medication history to confirm all inclusion criteria are met and that there are no exclusion criteria present. During these visits they will have urine testing for sodium and osmolality. Every other week, they will receive a phone call from study staff to discuss their experience using the study drug and monitor for any adverse effects. They will complete the Tinnitus Functional Index questionnaire over the phone as well. When the subjects come in for their study visit, 4 weeks after the baseline period, they will receive enough study medication for the rest of the study, to allow for randomization to placebo or active drug at that time.

4.2 Study Endpoints

4.2.1.1 Primary Study Endpoints

The primary outcome measurement will be the collective area under the Visual Analog Scale (VAS) curve above the week 3 baseline as assessed from week 3 to week 6 of the double blinded study phase.

4.2.1.2 Secondary and Exploratory Study Endpoints

Secondary endpoints will consist of safety and tolerability metrics including adverse event incidence and severity, regimen adherence and voluntary study drop-out rates reported during the non-blinded and blinded study phases. The frequency and percentage of each secondary measure will be determined for the non-blinded study phase and by study arm for blinded study phase. Additionally, any changes in THI greater than 1 grade will be determined from week 3 to week 6 of the double blinded study phase. The frequency and percentage of these changes will be summarized by study arm.

A descriptive summary using means and standard deviations stratified by dosage group for the treatment subgroup during the blinded study phase will be performed. The partial eta squared effect size difference will be estimated.

5 Study Enrollment and Withdrawal

Patients older than 18 years old are able to participate. The maximum age of participants is 75 years old. The racial and ethnic origin will reflect the demographics of the populations that seek evaluation of tinnitus at NYU Langone Medical Center.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age ≥18 years
2. Continuous perception of subjective tinnitus for ≥ 6 months duration
3. Evidence of a normal otolaryngologic evaluation within the past year with no evidence of otitis media or externa
4. THI of ≥ 16
5. Tinnitus loudness rating of ≥4/10

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Treated for tinnitus < 6 months due to the acute nature of their condition and slight handicap according to the Tinnitus Handicap Inventory Severity Scale.
2. Tinnitus of a muscular or vascular etiology
3. Conductive hearing loss
4. History of migraine
5. History of pulmonary edema
6. History of congestive heart failure
7. History of severe renal disease
8. Prior use of oxytocin nasal spray
9. Latex allergy
10. Women who are currently breastfeeding
11. Pregnancy

Because tinnitus may be co-morbid with migraine, and because migraine may be responsive to treatment with intranasal oxytocin, patients who suffer from migraines will be ineligible to participate. As patients who are allergic to latex may react to the oxytocin spray, individuals with this allergy will be ineligible to participate in the study.

5.3 Vulnerable Subjects

Prisoner-patients will not be approached for participation due to federal and state requirements governing participation of prisoners in research. Pregnant women and individuals with impaired decision-making capacity also will not be approached for this study.

5.4 Strategies for Recruitment and Retention

We will recruit patients from NYU Langone Medical Center's Departments of Otolaryngology and Neurology. We will aim to recruit and enroll 50 patients with a goal of 30 study participants remaining after accounting for some screen failures. Subjects will be identified for study inclusion through otolaryngologists' and neurologists' referrals of patients with tinnitus.

An IRB-approved dear provider letter will be sent to providers from NYU Departments of Otolaryngology and Neurology to assist in identifying potential study participants for referral to the study team. A member of the study team will contact the individual for screening for the study. Data including patient initials, age, date of birth, menstrual status (if applicable), allergies, prior history of migraine, tinnitus quality, severity, duration, ENT evaluation, and current medications will be used for subject identification, informing subjects, and initial discussion of subject eligibility. Information will be obtained through review of medical records and direct interview. The Principal Investigator will review the informed consent form with the potential participant. The Principal Investigator and Research Coordinator will have access to identifiable information as needed for recruitment of study participants. Emails will be securely sent to potential participants via send safe.

5.4.1.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify subjects. The PI and Research Coordinator will have access to the EPIC search results.

Any recruitment information sent by email will utilize Send Safe email.

Once potential subjects have been identified, the study team will notify the treating physician (TP) that they have patients eligible to participate as follow:

- TP has been notified that the study team will contact potential subjects directly, by letter, phone, email, or the MyChart portal etc.

Once contact is made, approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.5 Duration of Study Participation

The study will last about 4 months and will involve about 17 visits. This includes the consenting process, screening procedures and all study visits.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 50 participants are enrolled. It is expected that approximately 50 participants will be enrolled in order to produce 30 evaluable participants. These participants between the ages of 18 and 75 are to be entered into this study at NYU Langone Medical Center. This research project will only be taking place at this site. This study will be an out-patient study. The study visits will be at the NYU Langone Preston Robert Tisch Center for Men's Health, 555 Madison Avenue, 3rd Floor, New York, NY 10022.

5.7 Participant Withdrawal or Termination

5.7.1.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- At any point during the study, a subject is found to have abnormal urine sodium or osmolality levels or an abnormal comprehensive metabolic panel
- They experience a significant rise in blood pressure (>150/100) or intolerable side effects (nausea, vomiting, headache, or significant worsening of tinnitus)

5.7.2 Handling of Participant Withdrawals or Termination

Subjects may withdraw from the study at any time. Subjects that choose to withdraw early from the study will be voluntarily surveyed for reasons for withdrawal. They will be asked for permission to continue to utilize the data collected up to the point of withdrawal for research purposes. Should they decline, all data past the note of withdrawal will be deleted from the record system. Subjects will be required to return any unused samples of nasal spray.

We will reach out to those withdrawn or terminated participants or those who discontinue the study agent but remain in the study for follow-up via 3 phone calls to them. Should participants not respond to our phone calls, a certified letter will be sent to their home address. For those participants who withdrew because of AEs, we will try to continuously follow them until AEs resolve.

We plan to replace participants who withdraw or discontinue the study early, in order to collect the minimum data required to determine the efficacy of the study drug, per Section 9.3 of the Statistical Considerations for the study, Analysis Datasets.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the investigator to the IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

6 Study Agent

6.1 Study Agent(s) and Control Description

The investigational product, oxytocin nasal spray (45 units/0.1mL for 100mL) is composed of: oxytocin 10 unit/MG/mannitol trituration (4.500g), magnesium chloride crystals (6.080g), citric acid anhydrous gran. (0.284g), sodium citrate powder (5.660g), sterile water for irrigation (100.000mL), and Pcca Mucolox liquid base(10.000mL).
See Oxytocin Nasal Spray package insert (29).

The placebo nasal spray consists of: magnesium chloride crystals (6.080g), citric acid anhydrous gran. (0.284g), sodium citrate powder (5.660g), sterile water for irrigation (100.000mL), and Pcca Mucolox liquid base (10.000mL). Both placebo and active drug will be handled and stored the same way.

6.1.1 Acquisition

The study agent and placebo will be prepared and acquired from VLS Pharmacy/New Drug Loft. They will be shipped to the study site at the Center for Men's Health, 555 Madison Avenue, 3rd Floor, New York, NY 10022.

6.1.2 Formulation, Appearance, Packaging, and Labeling

This nasal spray will be a liquid prepared at VLS Pharmacy/New Drug Loft and contained in 30mL amber glass bottles with nasal sprayers. Both active drug and the placebo will appear identical in the glass bottles. These bottles will be labeled with subject specific labels to be marked by the study coordinator. The label will also say "Oxytocin/Placebo." This study medication is investigational and will be formulated specifically for the purpose of meeting the trial plan.

6.1.3 Product Storage and Stability

Study agent and placebo will be stored in amber glass bottles in a secure refrigerator that only study personnel will have access to. The medications will be kept between 36°F to 46°F (2°C - 8°C). They cannot be frozen or exposed to direct light. After its preparation, the study agent is good for 30 days in the refrigerator. It must be kept out of the reach of children.

6.1.4 Preparation

The study drug and placebo nasal sprays will be mixed/prepared by VLS Pharmacy/New Drug Loft and shipped to the study site. They can be contacted at (718)854-3061.

6.1.5 Dosing and Administration

After the baseline period of the study (1 week), subjects will receive intranasal oxytocin for 9 weeks. They will receive a spray bottle with study medication at Visit 3 to be self-administered at home four times per day (9AM, 1PM, 5PM, and 9PM). They will be instructed to apply 1 puff (the equivalent of 30 to 45 oxytocin IU) in one nostril four times per day, equivalent to 120 to 180 IU per day.

Subjects will be shown the proper way to use the nasal spray and administer the study medication. With their head facing forward, not tilted up or down, they should place the sprayer in one nostril and spray once while holding their breath. They should then pinch both nostrils closed for 5 seconds. They will be instructed not to sniff in or blow their nose for at least 5 minutes after administration. During the following 6 weeks of the study, subjects may receive placebo or oxytocin nasal spray. The placebo will be administered in the same manner as the active study drug, with 1 puff in one nostril four times per day (9AM, 1PM, 5PM, and 9PM). If the subject is randomized to the active drug during this phase, their dose will be the same dose they received during Week 9 of the study, during the non-blinded phase.

The nasal spray should be refrigerated when not being used. Subjects will also have a re-freezable bag to store their spray bottles in when not near a refrigerator.

6.1.6 Route of Administration

The route of administration for the study medication is intranasally.

6.1.7 Starting Dose and Dose Escalation Schedule

All subjects will begin at a dose of 30 IU 4 times daily for 2 weeks. If no response is reported (defined as a decrease in VAS of < 2), they will have the dose increase by 5 IU per spray every 2 weeks, until a maximum dose of 45 IU 4 times daily. If patients report improvement (defined as improvement in VAS >3) at any dose, they will remain at that dose through the end of the second phase. In the event that the patient experiences a moderate side effect, the dose will be decreased to the previous dose for the remainder of this phase.

Subjects will be informed that depending on their responses, their dose may stay the same, be increased or decreased. Accordingly, after Visit 3, active drug will be dispensed at office study visits every 2 weeks during the non-blinded phase.

The dose for the oxytocin nasal spray will be 30, 35, 40, or 45 IU per puff to be administered four times per day. This dosage was determined by treating 2 patients (as described above) with tinnitus in our clinical practice. Both patients were initially treated with 16 IU oxytocin nasal spray daily as detailed in the Azevedo et al study (5). Both patients noted slight improvement, and over the course of several months the dose was gradually increased while following their clinical course and vital signs and laboratory studies. Maximum benefit was noted at a dose of 45 IU QID.

6.1.8 Dose Adjustments/Modifications/Delays

As stated in Section 6.1.7, dose changes will be made according to subjects' responses. Any subjects that experience moderate side effects will have their dose lowered to the previous dose for the remainder of that study phase. If a subject is found to have urine electrolyte (sodium) or osmolality abnormalities during study visits, study medication will be discontinued and the subject will have to withdraw from the study.

6.1.9 Duration of Therapy

The study consists of 3 phases:

1. 1 week baseline period during which no study medication will be administered.
2. 9 week non-blinded phase during which all subjects receive oxytocin nasal spray (30 – 45 IU four times/day)
3. 6 week "double-blind" phase during which half the subjects receive oxytocin nasal spray (up to 45 IU four times/day) or the placebo nasal spray.

6.1.10 Tracking of Dose

Subjects will be asked to bring their study medication bottles in to each office study visit, every other week. They will also be asked to complete a daily tinnitus severity log that will also ask if they have taken each dose that day.

6.2 Study Agent Accountability Procedures

After the compounding pharmacy prepares and delivers the active drug and placebo, the study coordinator will have access to the secure refrigerator where study drug is stored. At Visits 3, 5, 7, and 9, she will distribute the study agent (oxytocin nasal spray) to each participant. The participants will receive only enough of the study agent for the next 2 weeks of the study. They will have to return to the office at weeks 11 and 13 to receive study drug or placebo for the double blind phase of the study.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on a drug accountability log, and signed and dated by the study team.

Subjects will receive a phone call from the study coordinator to discuss the subject's experience using the study drug the prior week. Subjects will also have to complete a daily log noting the severity of their tinnitus for that day and the time they took their medication. Study staff will review this information at each visit, every other week.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Patients will come to the Preston Robert Tisch Center for Men's Health for study visits every 2 weeks and be administered the VAS and THI/CGI scales by the research coordinator or principal investigator. The screening visit will be the most comprehensive and include obtaining informed consent, a physical exam with vital signs, laboratory studies, questionnaires, an ECG, and review of medical and medication history

to confirm all inclusion criteria are met and that there are no exclusion criteria present. During these visits they will have urine testing for sodium and osmolality. Every other week, they will receive a phone call from study staff to discuss their experience using the study drug and monitor for any adverse effects. They will complete the Tinnitus Functional Index questionnaire over the phone as well. When the subjects come in for their study visit, 4 weeks after the baseline period, they will receive enough study medication for the rest of the study, to allow for randomization to placebo or active drug at that time.

7.1.1 Study Specific Procedures

Visit Details

Visit	Visit Type	Procedures	Labs	Questionnaires	
Screening (Week 0)	Office visit	Obtain informed consent, review of medical and medication history, physical exam, vital signs, ECG	Comprehensive metabolic panel, urine electrolytes & osmolality, urine pregnancy test	X	
Baseline (beginning of Week 1)	Phone	Review of current medications, issue daily VAS log		X	Baseline
End of Week 1	Office visit	Review of current medications, dispense active drug, review VAS log	Urine pregnancy test	X	Non-Blinded Phase
Week 2	Phone	Review of current medications		X	
Week 3	Office visit	Review of current medications, study drug reconciliation, dispense active drug, study log review	Urine electrolytes & osmolality, urine pregnancy test	X	
Week 4	Phone			X	
Week 5	Office visit	Review of current medications, study drug reconciliation, dispense active drug, study log review	Urine electrolytes & osmolality, urine pregnancy test	X	
Week 6	Phone	Review of current medications		X	
Week 7	Office visit	Review of current medications, study drug reconciliation, dispense active drug, study log review	Urine electrolytes & osmolality, urine pregnancy test	X	
Week 8	Phone	Review of current medications		X	
Week 9	Office visit	Review of current medications, randomize & dispense new drug, study log review	Urine electrolytes & osmolality, urine pregnancy test	X	
Week 10	Phone	Review of current medications		X	

Week 11	Office visit	Review of current medications, study drug reconciliation, dispense study drug, study log review	Urine electrolytes & osmolality, urine pregnancy test	X	Double Blind Phase
Week 12	Phone	Review of current medications		X	
Week 13	Office visit	Review of current medications, study drug reconciliation, dispense study drug, study log review	Urine electrolytes & osmolality, urine pregnancy test	X	
Week 14	Phone	Review of current medications		X	
Week 15	Office visit	Review of current medications, study drug reconciliation, study log review	Comprehensive metabolic panel, urine pregnancy test	X	

7.1.2 Clinical Laboratory Evaluations

- **Blood tests: Comprehensive Metabolic Panel (CMP) at the screening visit (as abnormal values will exclude patients from the study) and final study visit**
- **Urinalysis:** dipstick urinalysis, including electrolyte levels and urine concentration; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.
- **Pregnancy test**, female subjects of childbearing potential will undergo a urine pregnancy test every week that an office study visit occurs.

7.1.3 Specimen Preparation, Handling, and Storage

Labeled urine samples will be taken the same day to the Tisch Laboratory for processing. Labels will include the participant's initials, subject ID number, and date and time the sample was obtained.

7.2 Study Schedule

7.2.1 Screening

Screening Visit

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medication history to determine eligibility based on inclusion/exclusion criteria.
- Obtain demographic information, alcohol and tobacco use history.
- Perform medical examinations and ECG needed to determine eligibility based on inclusion/exclusion criteria.
- Draw blood for CMP to determine eligibility.
- Collect urine for electrolyte levels, urine osmolality, and pregnancy test if applicable.
- Perform questionnaires including the Tinnitus Handicap Inventory (THI), Clinical Global Impression (CGI) for baseline, and suicidality history.
    - Due to the correlation between tinnitus and suicide, the investigator will evaluate suicidality history by patient interview to be recorded in the CRF. This will be re-assessed at follow up visits as a part of the THI. If a subject reports suicidal ideation or intent at any time, they will immediately be referred to a psychiatrist or psychiatric emergency department.
- Schedule study visits for participants who are eligible and available for the duration of the study.

7.2.2 Enrollment/Baseline

Visit 2: Baseline Visit – Beginning of Week 1 (Phone Visit)

- Review of current medications.
- Administer THI and VAS questionnaires.
- Issue daily Tinnitus Severity Log/Visual Analog Scale (VAS) log by email.

7.2.3 Intermediate Visits

7.2.3.1 Visit 3: End of Week 1 (Office Visit)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Perform urine pregnancy test, if applicable.
- Administer THI questionnaire.
- Provide the study medication to the participant to use four times daily for the next 2 weeks.

7.2.3.2 Visit 4: Week 2 (Phone Visit)

- Review current medications.
- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.3.3 Visit 5: Week 3 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Collect urine for electrolyte levels and urine osmolality. Perform urine pregnancy test, if applicable.
- Administer THI and Clinical Global Impression – Improvement (CGI-I) questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Study drug reconciliation and record of participant's adherence to treatment program.
- Provide the study medication to the participant to use four times daily for the next 2 weeks.

7.2.3.4 Visit 6: Week 4 (Phone Visit)

- Review current medications.
- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.3.5 Visit 7: Week 5 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Collect urine for electrolyte levels and urine osmolality. Perform urine pregnancy test, if applicable.
- Administer THI and Clinical Global Impression – Improvement (CGI-I) questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Study drug reconciliation and record of participant's adherence to treatment program.
- Provide the study medication to the participant to use four times daily for the next 2 weeks.

7.2.3.6 Visit 8: Week 6 (Phone Visit)

- Review current medications.

- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.3.7 Visit 9: Week 7 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Collect urine for electrolyte levels and urine osmolality. Perform urine pregnancy test, if applicable.
- Administer THI and Clinical Global Impression – Improvement (CGI-I) questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Study drug reconciliation and record of participant's adherence to treatment program.
- Provide the study medication to the participant to use four times daily for the next 2 weeks.

7.2.3.8 Visit 10: Week 8 (Phone Visit)

- Review current medications.
- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.3.9 Visit 11: Week 9 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Collect urine for electrolyte levels and urine osmolality. Perform urine pregnancy test, if applicable.
- Administer THI and CGI-I questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Study drug reconciliation and record of participant's adherence to treatment program.
- Randomize and dispense new study drug (active drug or placebo nasal spray) to use for the next 2 weeks.

7.2.3.10 Visit 12: Week 10 (Phone Visit)

- Review current medications.
- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.3.11 Visit 13: Week 11 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Collect urine for electrolyte levels and urine osmolality. Perform urine pregnancy test, if applicable.
- Administer THI and CGI-I questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Provide the study medication to the participant to use four times daily for the next 2 weeks.

7.2.3.12 Visit 14: Week 12 (Phone Visit)

- Review current medications.

- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.3.13 Visit 15: Week 13 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Collect urine for electrolyte levels and urine osmolality. Perform urine pregnancy test, if applicable.
- Administer THI and CGI-I questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Provide the study medication to the participant to use four times daily for the next 2 weeks.

7.2.3.14 Visit 16: Week 14 (Phone Visit)

- Review current medications.
- Assess and record adverse events including dyspnea as reported by participant or observed by investigator.
- Record participant's adherence to treatment program.
- Administer phone Tinnitus Functional Index (TFI) questionnaire.

7.2.4 Final Study Visit

Visit 17: Week 15 (Office Visit)

- Record vital signs and auscultate lungs.
- Review current medications and results of VAS log.
- Draw blood for CMP to be able to compare to baseline levels.
- Perform urine pregnancy test, if applicable.
- Administer THI and CGI-I questionnaires.
- Record adverse events as reported by participant or observed by investigator.
- Study drug reconciliation and record of participant's adherence to treatment program.

7.2.5 Withdrawal/Early Termination Visit

If the participant agrees, any participant who withdraws from the study or is terminated early, will be asked to come in for a final visit in which we will record vital signs, obtain blood for CMP, record adverse events, and review results of VAS, THI and CGI.

7.2.6 Unscheduled Visit

In the event of an unscheduled patient visit, the subject will undergo safety screening – a focused physical exam, and blood pressure, temperature, and heart rate documentation. Depending on the reason for the visit, the subject may be referred to the appropriate service for possible adverse event follow up. All adverse events reported by the subject or observed by the investigator will be documented and reported. Aside from adverse events, information gathered at these unscheduled visits will not be included in the statistical analysis.

7.3 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications. Review of concomitant medications will occur at every phone and office visit.

7.4 Prohibited Medications, Treatments, and Procedures

Current medications are reviewed at each visit. If at any point during the study, a participant begins taking dinoprostone or ephedrine, they must stop taking the prohibited medication in order to continue participating in the study.

7.5 Participant Access to Study Agent at Study Closure

At study end, participants will not be provided additional samples of study medication.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At

each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Unexpected, related, and harmful adverse events will be reported to the IRB within 10 working days of discovery. Subjects will be followed until the resolution of the adverse event.

8.4.2 Serious Adverse Event Reporting

In addition to determining the appropriate intervention and ensuring the subject is medically treated, all serious adverse events will be reported to the IRB within 24 hours of discovery.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the principal investigator's responsibility to report UPs to the IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP promptly, within 2 weeks of the IR's receipt of the report of the problem from the investigator.

8.5 Study Halting Rules

Administration of the study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the PI. The PI will notify the IRB immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants and the active participants will be contacted via phone and if necessary certified mail, to immediately discontinue the spray.

8.6 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

An independent licensed physician who is a specialist in neurology or otolaryngology will be appointed to monitor subject safety. Scott Grossman, MD of the Department of Neurology will perform this role; Dr. Grossman is a disinterested third party and is well acquainted with good research practices. In addition to individual subject monitoring at each visit, the PI will systematically review accumulated data, adverse events, and other relevant events in the study: (1) assess the timeliness, completeness, and quality of the data collected, (2) assess the adherence to protocol requirements, especially measures taken to protect participant safety, and (3) assess the benefit/risk ratio of study procedures monthly.

A summary of AEs and outcomes of these monthly reviews will be submitted to the IRB every 6 months. The PI and Dr. Grossman will meet and review data after every 15 subjects have been enrolled, and will be provided with the following data prior to this meeting: (1) all adverse events reported, and (2) subject recruitment, enrollment, and dropout numbers. During the meeting, they will review these data and have 30 days to generate a report, which reflects their opinion of whether the study should be permitted to continue and whether any changes need to be made. This report will then be submitted to the IRB. If any serious adverse events occur during the study, Drs. Newman and Grossman will be apprised of them within 24 hours of the event and will be provided unblinded information with regard to the participants' treatment assignment and corresponding study visit. They will then provide suggestions for the progress of the study, as well as determine whether modifications to the protocol are needed. Any additional events of pulmonary edema will be reported to the IRB as Reportable New Information, as per NYU SOM IRB policy.

Patients will be screened for depression and suicidality at the screening visit and during the weekly follow-up visits via direct questioning and in the THI (questions 5 and 21). Any patient with worsening depression or suicidal ideation will be immediately referred to their psychologist/psychiatrist or the psychiatric emergency department. The PI will personally call the appropriate person (clinician, ED, or emergency services) as deemed appropriate for the individual subject. Although there have been reports in the literature linking low plasma and CSF oxytocin levels with suicide, oxytocin nasal spray has been demonstrated to have antidepressant and anxiolytic effects, and as such, we do not expect treatment to worsen depression, but rather improve mood.

9 Statistical Considerations

9.1 Plans (SAP)

The primary analysis is to provide an estimate of the partial eta squared effect size difference between placebo and treatment during the blinded phase of the study as well as to provide initial safety and tolerability estimates during the initial open label study phase. The effect size will be calculated and interpreted using η^2=0.2 as a small effect, η^2=0.5 as a medium effect, and η^2=0.8 as a large effect (20).

9.2 Statistical Hypotheses

We hypothesize that treatment with high dose oxytocin nasal spray will result in a large effect size as measured by partial eta squared for the difference in mean area under the curve in baseline adjusted VAS when compared to placebo during the blinded study phase.

The primary outcome measurement will be the collective area under the VAS curve above the week 3 baseline as assessed from week 3 to week 6 of the blinded study phase. The area under the curve will be determined using the linear trapezoidal method for each participant after subtracting the baseline (week 3) VAS value from each subsequent measure to determine the collective improvement/decline of the VAS measurement during the blinded study phase. The mean and standard deviation of the total area will be

calculated for each study arm (active drug and placebo) and partial eta squared effect size for the difference determined. This effect size estimate can then be used to power future comparative studies.

The same area under the curve above the baseline VAS metric will be determined separately for the non-blinded/open label study phase. The inherent bias of non-blinding may influence this metric although the relatively larger sample size (n=30) could also improve precision. Therefore, the area will be presented as a descriptive summary using the mean and standard deviation with an effect size estimate.

Secondary endpoints will consist of safety and tolerability metrics including adverse event incidence and severity, regimen adherence and voluntary study drop-out rates reported during the non-blinded and blinded study phases. The frequency and percentage of each secondary measure will be determined for the non-blinded study phase and by study arm for blinded study phase. Additionally, any changes in THI greater than 1 grade will be determined from week 3 to week 6 of the blinded study phase. The frequency and percentage of these changes will be summarized by study arm.

9.3 Analysis Datasets

Efficacy data will be analyzed for all subjects who received at least one dose of study-drug and provided at least one endpoint measurement during the non-blinded study phase. For the blinded study phase efficacy data will similarly be analyzed for all randomized patients providing at least one endpoint measurement. A separate per protocol patient population defined as patients providing complete efficacy data will also be defined for each study phase.

Safety and tolerability data will be analyzed for all enrolled patients receiving at least one dose of study-drug during the non-blinded study phase and then for all randomized participants during the blinded study phase.

9.4 Description of Statistical Methods

Data from this pilot study will be summarized separately for the non-blinded study phase and by study arm for the blinded study phases. The area under the VAS curve after subtracting baseline value will be determined using the linear trapezoidal method. These areas will be determined for the efficacy population using the last observation carried forward (LOCF).The mean and standard deviation for the non-blinded phase will be determined and the effect size for the mean area from zero calculated. For the blinded phase week 3 (after a 2 week “washout”) will serve as the baseline and the area under the VAS curve from baseline will be calculated using LOCF imputation for missing post baseline data. To avoid potential cross-over effects from the 9 week non-blinded phase when all subjects receive active drug, after randomization, subjects will receive either active drug or placebo. The first 2 weeks of this 6 week period will be a washout period from statistical analysis. While subjects will still receive study drug, data collection for that phase will not begin until week 3 of that 6 week period. The mean and standard deviation in area under the VAS curve from baseline for each study arm will be determined and the partial eta effect size for the mean difference between study arms calculated. This summary will be performed for the per protocol study population as well to investigate the relative influence of missing data on the effect size determination.

Frequencies and percentages for the secondary safety and tolerability endpoints will be determined using the ITT patient population for the non-blinded study phase and all randomized participants during the non-blinded study phase. The other secondary endpoint, incidence of the change in THI of 1 point or greater, will be summarized by study arm for those participants providing at least 1 post-week 3 baseline THI measurement.

The analyses will be refined and adjusted in anticipation of study termination and data lock.

9.4.1 General Approach

The study design is a pilot, proof of concept, two-phase study. The first non-blinded study phase is to provide tolerability, regimen adherence, and initial safety data for the active treatment. The second phase after 2 week washout allows for efficacy comparison of the mean VAS difference from baseline between

active drug and placebo and incidence of THI changes greater than 1 point. Please see Schematic of Study Design.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the area under the VAS curve from baseline for all randomized participants during the blinded study phase. The week 3 data after two week washout will serve as the baseline and the interval/ratio scaled area determined using the linear trapezoidal method. The expectation is that placebo participants' post-baseline VAS data will remain relatively consistent with baseline values while active treatment will trend post-baseline. Using an LOCF imputation strategy is therefore a conservative strategy for handling missing data by understating trending in the active treatment group without introducing trending in the placebo group. The mean and standard deviation by study arm in the area under the VAS curve from baseline will be presented along with the partial eta squared effect size estimate for the mean difference between study arms. The availability of data will be determined by study arm at each post-baseline study time point during the blinded study phase to investigate the potential influence of missing data. A per-protocol analysis will also be presented to further investigate the influence of missing data on the primary efficacy endpoint.

The area under the VAS curve from baseline will similarly be determined and analyzed separately for the open label/non-blinded study phase. Since this measure is biased by participant knowledge of treatment the effect size of the mean VAS area from baseline will be determined and cautiously interpreted.

As included in Section 9.1, the effect size will be calculated and interpreted using η^2=0.2 as a small effect, η^2=0.5 as a medium effect, and η^2=0.8 as a large effect (20). These cut-offs will be used to judge the strength of the treatment relative to placebo control with medium ($\eta^2 \geq 0.5$) considered a treatment "success."

9.4.3 Analysis of the Secondary Endpoint(s)

Frequencies and percentages for the secondary safety and tolerability endpoints will be determined using the ITT patient population for the non-blinded study phase and all randomized participants during the non-blinded study phase. Patients withdrawing prematurely from the study will be summarized by study timepoint and phase (blinded/non-blinded) and study arm (if applicable) and reason if available. The total number of adverse events (AE) will be summarized by severity, drug-relatedness, and whether it is an SAE and then also the total number of participants experiencing an AE will be summarized by study phase and/or study arm. Adherence to treatment regimen will be determined by the percentage of treatment ingested per the prescribed treatment amount at each evaluable study time point. Mean adherence will be determined at each study time point during the non-blinded study phase and by study arm during the blinded phase. The other secondary endpoint, incidence of the change in THI of 1 point or greater, will be summarized by study arm for those participants providing at least 1 post-week 3 baseline THI measurement.

9.4.4 Safety Analyses

The total number of adverse events (AE) will be summarized by severity, drug-relatedness, and whether it is an SAE and then also the total number of participants experiencing an AE will be summarized by study phase and/or study arm.

9.4.5 Adherence and Retention Analyses

Adherence to treatment regimen will be determined by the percentage of treatment insufflated per the prescribed treatment amount at each evaluable study time point. Mean adherence will be determined at each study time point during the non-blinded study phase and by study arm during the blinded phase. Each subject's medication use and study diary will be reviewed at every visit to measure adherence Patients withdrawing prematurely from the study will be summarized by study timepoint and phase (blinded/non-blinded) and study arm (if applicable) and reason if available.

9.4.6 Baseline Descriptive Statistics

Descriptive summaries will be performed separately for the non-blinded study phase and by study arm for the blinded study phase using means, standard deviations, and frequencies and percentages. There will be no inferential statistics used as randomization should eliminate the potential for bias.

9.4.7 Planned Interim Analysis

Not applicable

9.4.7.1 Safety Review

Administration of the study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the PI. The PI will notify the IRB immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants and the active participants will be contacted via phone and if necessary certified mail, to immediately discontinue the spray.

9.4.7.2 Efficacy Review

Not applicable

9.4.7.3 Additional Sub-Group Analyses

Not applicable

9.4.7.4 Multiple Comparison/Multiplicity

Not applicable

9.4.7.5 Tabulation of Individual Response Data

Not applicable

9.4.7.6 Exploratory Analyses

Changes in CGI and TFI from baseline (week 3) to week 6 during the blinded study phases will be determined and summarized using means and standard deviations for each study arm. A descriptive summary using means and standard deviations stratified by dosage group for the treatment subgroup during the blinded study phase will be performed. The partial eta squared effect size difference will be estimated.

9.5 Sample Size

This is a pilot, proof of concept study with the main goal of providing an estimate of the effect size difference between treatment and placebo control. As such the sample size of n=30 will provide sufficient estimates of the effect sizes necessary to power a future two-armed randomized study

9.6 Measures to Minimize Bias

9.6.1.1 Enrollment/Randomization/Masking Procedures

After receiving intranasal oxytocin for 9 weeks, participants will be randomized to either intranasal oxytocin or placebo. The fellow will use a random number generator to assign subjects to 0 (placebo) or 1 (active drug) each time a subject enters the randomized phase of the study. He will use block randomization so that treatment group assignments are balanced. This information will be created and stored in the Randomization Log. This will be kept securely, stored in a separate Randomization binder to ensure the non-blinded fellow only accesses the information as needed to randomize the study medication at visit 11.

9.6.1.2 Evaluation of Success of Blinding

Not applicable

9.6.1.3 Breaking the Study Blind/Participant Code

The blind shall not be broken until the final data analysis, however:

All adverse events (AEs) occurring during the course of the clinical drug trial will be brought to the attention of the PI. For significant AEs and serious adverse events (SAEs), the PI will decide on an appropriate intervention. Most AEs should not normally lead to the breaking of the treatment assignment code. However, if the AE is so severe that it significantly compromises the well-being of the subject, the PI may decide to break the blindness code and withdraw the subject from the study.

In the case of AEs of intermediate severity, as when a certain laboratory parameter or clinical sign or symptom gradually deviates from normality, the PI will treat these deviations using standard and well accepted treatment guidelines and continue to follow the patient until said abnormalities resolve. If standard treatments fail to resolve the abnormalities, the PI may decide to break the blind.

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of auditing, and inspection by local and regulatory authorities.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent material is submitted with this protocol: Key Information.

12.3.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. Subjects will be consented by the Principal Investigator, in his office, when they come in for their initial appointment before any study procedures can be completed. The PI will be able to answer any questions the individual has about participation in the study including the potential risks and benefits. The investigator will explain the research study to the participant and answer any questions that may arise.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

None of the subjects enrolled in the study will have impaired decision-making capacity. Only patients who are able to provide their own informed consent will be able to participate in this study. Subjects will be asked to explain their understanding of participation in the study. The PI will encourage questions as well as ask open – ended questions about study procedures. The investigator will reaffirm the subject's willingness to participate in the study, making sure it is understood that their participation is voluntary.

The original signed consent form will be stored on file at the Preston Robert Tisch Center for Men's Health with dates documented on the Pre-Screening Log, Study Subject Tracking Log, and Screening Visit Log source document. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

12.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

12.4.1.1 Research Use of Stored Human Samples, Specimens, or Data

The investigators and research coordinator will take necessary steps to maintain confidentiality of data. Paper documents with any personal health information will be stored securely in locked file cabinets when not in use. These and electronic data will only be handled by trained study team members when actively being used for research. Study staff will code data when appropriate and store data on RedCap, in compliance with NYU Langone policies.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to

register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14 Study Finances

14.1 Costs to the Participant

No costs to the participant.

15 Study Administration

15.1 Study Leadership

The Study Team will govern the conduct of the study. The Study Team will be composed of the PI, Medical Fellow, and Research Coordinator.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 References

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18 Schedule of Events

Activity	**Screening Visit** (Week 0)	**Baseline Visit** (Start of Wk 1) *Phone*	**Visit 3** (End of Wk1)	**Visit 4** (Wk2) *Phone*	**Visit 5** (Wk3)	**Visit 6** (Wk4) *Phone*	**Visit 7** (Wk5)	**Visit 8** (Wk6) *Phone*	**Visit 9** (Wk7)	**Visit 10** (Wk8) *Phone*	**Visit 11** (Wk9)	**Visit 12** (Wk 10) *Phone*	**Visit 13** (Wk 11)	**Visit 14** (Wk 12) *Phone*	**Visit 15** (Wk 13)	**Visit 16** (Wk 14) *Phone*	**Visit 17** (Wk 15)
Study team procedures																	
Consent	X																
Medical History	X																
Physical Exam	X																
Vital signs	X	X	X		X		X		X		X		X		X		X
Lung auscultation	X		X		X		X		X		X		X		X		X
Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation			X		X		X		X		X		X		X		
Randomization											X						
Participant study drug compliance check					X		X		X		X		X		X		X
Questionnaires	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiology assessments																	
Electrocardiogram	X																
Laboratory Assessments																	
Comprehensive Metabolic Panel	X																X
Urine electrolytes	X				X		X		X		X		X		X		
Urine osmolality	X				X		X		X		X		X		X		
Urine pregnancy test	X		X		X		X		X		X		X		X		X