A RANDOMIZED DOUBLE-BLIND 2-WAY CROSSOVER TRIAL TO ASSESS THE EFFICACY OF GUANFACINE AND LIDOCAINE COMBINATION VERSUS LIDOCAINE ALONE IN TRIGEMINAL NERVE BLOCK FOR PAIN MANAGEMENT IN PAINFUL TRIGEMINAL NEUROPATHY PATIENTS

Short Title: Efficacy of Guanfacine and Lidocaine combination in Painful Trigeminal Neuropathy Pain Management

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1.0 STUDY OBJECTIVE AND BACKGROUND

Study Objective:

The objectives of this study are to evaluate, in trigeminal nerve block procedures for painful trigeminal neuropathy adult patients between 18 and 80 years of age,

1. The efficacy of guanfacine in combination with lidocaine compared to lidocaine alone in extending the pain relief duration.
2. The safety and tolerability of a single dose of guanfacine in combination with lidocaine compared to lidocaine alone.

Background:

Painful trigeminal neuropathy is a severely painful condition affecting cranial nerve V (trigeminal nerve) that transmits sensation from the face. Painful trigeminal neuropathy affects one or more branches of the trigeminal nerve, most often the second (V2, maxillary) or third (V3, mandibular) division. The latest classification (ICHD-3) by the International Headache Society (IHS) distinguishes trigeminal nerve pain into trigeminal neuralgia and painful trigeminal neuropathy.[1] Classical trigeminal neuralgia includes cases that develop idiopathically or secondary to neurovascular compression.[1] Painful trigeminal neuropathy is caused by structural abnormalities or neural damage rather than vascular compression. Common causes of painful trigeminal neuropathy include multiple sclerosis, tumors, acute herpes zoster, post-chemotherapy neuritis, post-radiation therapy neuritis, and space occupying abnormalities. The pain associated with painful trigeminal neuropathy is highly variable in quality and intensity.[1] Painful trigeminal neuropathy is characterized by continuous or near-continuous facial pain often described subjectively as burning, squeezing, electrical, or likened to pins and needles.

The current treatment strategy for trigeminal neuralgia and painful trigeminal neuropathy includes the use of neuropathic pain medications (carbamazepine, oxcarbazepine, gabapentin, lamotrigine) and interventional procedures ranging from conservative local blocks to more invasive ablative procedures.[2–5] Traditionally, anticonvulsant and antidepressant medications are used to raise the threshold for neural signaling and reduce the severity of neuropathic pain sensed by the patient. Acute and chronic neuropathic pain treatment with these classes of medications is often insufficient, and opioids are added with the understanding of their accompanying risks and decreasing long-term benefits. Likewise, there are no supportive studies of chronic opioid use for functional improvement of trigeminal nerve pain. Medical management using neuropathic pain medications remains first line treatment for most patients, and progression to surgical or interventional management is not uncommon when standard medical therapy fails.[6,7] The decision to perform interventional or surgical procedures are based on many factors, including the patient's age, their overall health and ability to tolerate the procedure, the duration and intensity of pain and its impact on quality of life, and on patient preference.[8] Interventional procedures offered to patients with intractable trigeminal nerve pain often begin with diagnostic regional block with local anesthetic to ensure peripheral treatment of first-order neurons will adequately relieve the patient's pain. Further subsequent, **standard treatments include repeat regional blocks** with addition of adjunctive medications (i.e. steroids, clonidine, or botulinum toxin), or progression to trigeminal nerve ablation via radio-frequency or balloon compression, or radiotherapy.

Trigeminal nerve block using local anesthetic with or without adjuvants have been effective in relieving pain temporarily in some trigeminal neuralgia patients.[8–12] 2% lidocaine perineural injection (2-4 ml) in combination with neuropathic pain medications has been shown to be safe and effective in reducing pain, lowering the frequency of pain attacks, and reported improvement in the quality of life in classical trigeminal neuralgia patients.[13] High concentration (10% lidocaine) perineural injection with no adjuvant has been shown to be safe

and effective in reducing pain in certain trigeminal neuralgia patients.[8] After these blocks, pain often returns to previous levels of severity. The potential for more durable benefit from interventional blocks is, therefore, an unmet medical need. Importantly, adjuvants in combination with lidocaine, such as clonidine or dexamethasone, or other steroids have previously been shown to extend the duration of the block in other regional anesthesia techniques.[14,15] The proposed therapeutic approach is ultimately intended to generate durable relief of neuropathic pain without the potential side effects of steroids.

Alpha-2-adrenergic receptor function in managing pain

The alpha-2 adrenoreceptor has important roles in signaling within and between both the peripheral and central nervous systems. Stimulation of the alpha-2 adrenoreceptor suppresses calcium entry into the nerve terminal; it has been postulated that this dynamic is responsible for its inhibitory effect on secretion of neurotransmitters, leading to interruption of the propagation of pain signals.[16] Both central and peripheral alpha-2 adrenoreceptors are proposed to mediate interruption of pain signaling by this mechanism.[16] In humans, both the alpha 2A and 2B subtypes are expressed in the spinal cord and have been shown to be involved in antinociceptive activity.[17] Alpha-2 adrenergic agonists mitigate postoperative neuropathic pain in rats.[18–21]

Alpha-2 adrenergic agonists such as clonidine and dexmedetomidine have been successfully used as adjuvants to local anesthetics to extend by several hours, regional blocks used for surgical analgesia or acute and chronic pain treatment.[14] Clonidine (30 to 300 μg) is a well-known adjuvant for extending and enhancing the effect of local anesthetics.[15] Dexmedetomidine dose-dependently (4.5 to 13.5μg) enhances the local anesthetic action of lidocaine in inferior alveolar nerve blocks (IANB).[22] Clonidine (75 μg) with (10 ml) lidocaine, bupivacaine, and fentanyl has been used in trigeminal nerve block to manage pain in trigeminal neuralgia patients without significant adverse events.[23]

Guanfacine is the oldest alpha-2 adrenergic agonist in clinical use in this class.[24] Of the alpha-2 agonists, guanfacine has the lowest rate of sedation.[25] Guanfacine is currently approved in tablet form for the treatment of hypertension (1 to 2 mg) and Attention Deficit Hyperactivity Disorder (1 to 4 mg). Guanfacine is readily absorbed with around 80% oral bioavailability and has an elimination half-life of ~17 h with renal excretion accounting for ~50%.[26] Guanfacine has been shown to have similar *in vitro* potency as clonidine to inhibit conduction in rat sciatic nerve fibers.[27] Intrathecal guanfacine has a similar antinociceptive effect as that of intrathecal clonidine in a goat model.[28] Guanfacine showed longer antinociceptive effect in comparison to clonidine (8 h vs. 5 h) due to slower elimination of guanfacine from spinal cord tissue. In a rat model, intrathecal guanfacine has shown anti-nociceptive effect for greater than 18 h (both 25 mcg and 50 mcg) in comparison to clonidine injection (50 mcg) which declined to baseline within 4 h.[29] This study also reported a lower rate of elimination of guanfacine from spinal cord tissue compared to clonidine. Highly concentrated guanfacine (75 mcg in 15 μl saline) solution administered through an intrathecal route has been shown to be nontoxic in the subarachnoid space, establishing the safe use of guanfacine for perineural blockade.[30] Guanfacine as studied in animals and used in humans has a safe risk profile, suggesting that repurposing it for other indications. Guanfacine has the potential to be developed as a safe, non-opioid, analgesic for acute and chronic debilitating pain. Guanfacine in combination with 1% lidocaine is expected to be safe and to provide an extended duration of pain relief in painful trigeminal neuropathy patients who are not able to obtain pain relief from standard neuropathic pain medication.

PheWAS data indicating the role of the alpha-2-adrenergic receptor in trigeminal nerve pain

BioVU is a large repository of de-identified DNA samples that Vanderbilt University Medical Center (VUMC) has cataloged for >10 years from what otherwise would have been excess, discarded patient blood samples collected during routine clinical testing. Biospecimens within BioVU are linked to corresponding longitudinal clinical and demographic data derived from the Synthetic Derivative, our de-identified database of EMRs.[31–33]

Phenome-wide association studies **(**PheWAS) is a systematic and efficient approach to discover novel disease-variant associations and pleiotropy using BioVU, a centralized resource for investigating genotype-phenotype associations.[34] It is the comprehensive and diverse nature of the diagnostic information within EMRs that enables PheWAS. PheWAS not only replicates known genetic-phenotypic associations but also reveals new phenotypic associations with genetic variants, enhancing analyses of the genomic basis of human diseases and providing genetic support for drug discovery and drug repurposing efforts.[35–38]

Using PheWAS data we were able to identify a potentially use of guanfacine in treating trigeminal nerve pain. Genetic data from BioVU show that patients with a variant alpha 2B subtype receptor also have an increased likelihood of being diagnosed with trigeminal nerve disorders.

2.0 STUDY DESIGN

Primary Hypothesis:

Due to its different but relevant mechanism of action, guanfacine will be an effective adjunct to lidocaine in trigeminal nerve block for the treatment of painful trigeminal neuropathy by enhancing and prolonging pain relief compared to lidocaine alone.

Endpoints

The following endpoints will be measured to evaluate the exploratory objectives of the study assessing guanfacine and lidocaine in combination compared to lidocaine alone, in pain management in the painful trigeminal neuropathy patient.

- Primary endpoint: time to return to baseline pain (VAS) measurement after treatment with guanfacine as adjuvant to 1% lidocaine compared to 1% lidocaine alone
- Safety endpoint: comparable side effect profile of combination product compared to lidocaine alone on relevant adverse event measures: sedation, local site reaction, confusion
- Secondary endpoint: pain intensity after treatment to be measured throughout the follow-up periods on a visual analog scale (VAS)
- Secondary endpoint: quality of life after treatment to be measured using PROMIS Global Health -10 SF during the follow-up periods
- Secondary endpoint: frequency of acute trigeminal nerve pain attacks during the follow-up periods
- Secondary endpoint: total amount of rescue medications (opioid and non-opioid analgesics) for pain management during the follow-up periods
- Secondary endpoint: time to first rescue medication during the follow-up periods

Experimental Design

The trial is designed as a single-center, randomized, double-blind, controlle, 2x2 crossover pilot study with two arms: study drug (guanfacine and lidocaine combination) and active control (lidocaine alone). The target sample size is 30 study drug vs. 30 active control.

Not all participants that are randomized and initiate the first arm of the trial will *necessarily* complete *both* arms of the crossover trial. Based on previous experience, initiating the first arm of the cross over trial in 40 participants should be sufficient reach the full sample size (30 study drug vs. 30 active control). The trial will be complete and enrollment will cease upon reaching the full proposed sample size (30 study drug vs. 30 active control) .

Approximately 80 patients meeting preliminary enrollment criteria will be consented for screening with the goal of roughly half being eligible to randomize and begin participation in the trial.

Inclusion Criteria

- Adults between 18 and 80 years of age
- Ability to understand and read English
- History of painful trigeminal neuropathy with persistent background facial pain severity > 5/10 on VAS
- Experience pain with a score of greater than 5 on a 0-10 scale (VAS) in the previous 24 hours before procedural treatment and at the time of procedural treatment
- Eligible for trigeminal nerve block procedure and have not had a trigeminal nerve block procedure for pain management prior to enrollment in the current study
- Women of childbearing potential to provide agreement to use 2 forms of birth control while in the study
- Able to provide informed consent

Exclusion Criteria

- Presence of a significant structural lesion (e.g., tumor) as the cause of pain as shown in at least one neuroimaging study.
- Current diagnosis of fibromyalgia, temporomandibular disorders (TMD), odontogenic pain or other orofacial pain deemed unrelated to the trigeminal nerve as the origin.
- Allergy or any other hypersensitivity reactions to guanfacine or lidocaine or local anesthetic of the amide type, or to both iodinated contrast and gadolinium contrast.
- Females who are pregnant or breastfeeding and/or plan to become pregnant or to breastfeed during study participation.
- Inappropriately positive illicit drug test.
- Participation in another investigational drug study within 30 days before randomization.
- Inability to understand the requirements of the study, inability to abide by the study restrictions, inability to fill out the questionnaires, or inability to return for the required treatments.
- Any clinically significant medical or surgical condition that in the investigator's opinion could interfere with the administration of study drug, interpretation of study results, or compromise the safety or well-being of the subject (i.e. infection, unable to stop anticoagulants).
- No reliable access to telephone service to allow for contact with study personnel.

3.0 DRUG PRODUCTS

Study drug*:* Lidocaine 1% PF vials will be purchased from Pfizer. API grade guanfacine will be purchased from Procos S.p.A., and Vanderbilt University Medical Center's Investigational Drug Service will compound and dispense a 10 ml sterile syringe with a sterile locking syringe cap containing 6 ml 1% lidocaine with 250 mcg guanfacine (see **Appendix A** for mixing instructions).

Active control*:* The active control drug (6 ml 1% lidocaine sterile injection) will be dispensed by VUMC's Investigational Drug Service and will be identical in appearance to the study drug.

Mode of administration*:* Trigeminal nerve block procedure

Trigeminal nerve block will occur with the patient supine in the procedure suite. Based upon landmark and fluoroscopic image, the needle insertion site will be located and infiltrated with 1ml of 1% lidocaine. A 22-gauge stimuplex needle will be advanced under fluoroscopic guidance to the pterygoid fossa. Active stimulation at 0.75 mV will be used to confirm needle tip approaching the V2 maxillary branch of the trigeminal nerve and reduced to 0.3mV upon patient sensation. After confirming that the needle tip is in position with no sensation felt by the patient at <0.3mV, and after negative aspiration for blood or cerebral spinal fluid (CSF), 0.25ml of iodinated contrast (Omnipaque 300) or gadolinium-based contrast agent (Omniscan) if allergic to iodinated contrast will be injected under digital subtraction fluoroscopy to ensure no vascular uptake. If vascular uptake occurs, the needle tip will be adjusted, and tested again for vascular uptake. After confirmation of the needle placement, 3ml of the study drug or active control will be delivered. The needle will be retracted and angled toward the V3 mandibular branch of the trigeminal nerve and confirmed in the same method with fluoroscopy and stimulation as above. After confirmation of needle placement, the remaining 3ml of the study drug or active control will be deposited. The needle will then be removed. The patient will be taken to the recovery room and monitored for 60 minutes.

4.0 ENROLLMENT AND INFORMED CONSENT

The study will be discussed with patients identified as potential candidates by primary criteria (above inclusion/exclusion listing) to determine suitability and willingness to participate in the study. Study staff will provide participants the opportunity to consent to participate. Study staff will inform participants that participation is voluntary, and if they enroll, they may withdraw from the study at any time, for any reason. Participants will be given ample opportunity to ask questions and will have their questions answered.

MyResearchAtVanderbilt (MRAV) is a participant repository recruitment tool available to Vanderbilt researchers that reaches over 18,000 My Health at Vanderbilt users that have previously confirmed they would like to be contacted directly for research. This repository provides investigators a forum for advertising to volunteers for a specific study. Email notifications are limited to IRB approved language, describe study specifics and provide contact information. To utilize this initiative, investigators complete a MRAV Access Request that is reviewed to ensure the recruitment tool and requested number of contacts are appropriate. To facilitate engagement and inform this pool of patients that they be contacted about study participation, the Study Coordinator will send an email approved by the IRB and MRAV study team.

Research Notifications Distribution List: Researchers can provide potential participants information about their study using the Research Notification Distribution List. This is a recruitment tool available to Vanderbilt researchers that reaches over 18,500 Vanderbilt faculty and staff, as well as some members of the Middle Tennessee community To facilitate engagement and inform this pool of patients that they be contacted about study participation, the Study Coordinator will send an email approved by the IRB.

The study will utilize EHR reports to identify and contact participants using VICTR's EHR Recruitment tool(s), including My Health at Vanderbilt mass Direct-to-Patient messaging and custom Reporting Workbench Report to identify potential participants.

Reporting Workbench (RWB) Reports are available/viewable in eStar. These reports are developed using real-time data and can be customized to meet study-specific inclusion/exclusion criteria. Research team members with eStar access and access to the Report Groups can view/run the reports as frequently as needed. While the report is generally limited to certain variables, it provides easy access to a patient's record for additional screening and confirmation of eligibility. A custom RWB report will be utilized to identify potential participants. The report will filter on study inclusion/exclusion criteria computable in the EHR and will display variables requested by the

study team. Additional variables used to filter the cohort include for mass messaging include: Research OK to Contact status, MHAV account activation/message status.

My Health at Vanderbilt (MHAV) Mass Direct-to-Patient messaging uses the MHAV patient portal to message a predefined cohort of patients who meet certain study-specific inclusion/exclusion criteria, have explicitly said OK to Contact for research, and have an active MHAV account. The IRB-approved MHAV mass messages are sent by the VICTR EHR Recruitment Support Team, not the study team.Potential participants who have an explicit OK to Contact documented in eStar will receive the following message based on the patient's MHAV notification preferences. If email and/or text notifications for research are not checked, the study information will simply appear on their research studies page in MHAV.

5.0 STUDY PROCEDURE

The study is a single center, randomized, double-blind, 2 x 2 crossover pilot study with two arms; study drug (guanfacine and lidocaine combination) and active control (lidocaine alone). Adult participants between 18 and 80 years of age who have been diagnosed with painful trigeminal neuropathy will be consented for the study. The study includes three visits; an initial visit for evaluation, consent, and baseline surveys followed by two procedural visits. After each procedural visit data will be collected for 14 days. Participants will be randomized in permuted pairs (to ensure balance after every second enrollment) to receive either study drug (guanfacine and lidocaine combination) or active control (lidocaine alone) for the first nerve block procedure. Following the first procedural visit and 14-day follow up period, the study team will assess inclusion and exclusion criteria and (if eligible) schedule the second procedural visit.

Assessment	**Study Visit 1:** **Consent and screening** *(Day -15 to 0)*	**Study Visit 2:** **Procedure 1** *(Day 1)*	**Follow-up period 1** *(Day 2-14)*	**Study Visit 3:** **Procedure 2** *(≥15 days after procedure 1)*	**Follow-up period 2** *(14 days after procedure 2)*
Administrative Procedures					
Eligibility Review	X	X		X	
Informed Consent	X				
Demographics	X				
Pain History	X				
Baseline Pain	X	X	X	X	X
Medical History	X				
Concomitant Medications	X	X		X	
Surgical/ Past Treatments History	X				
Verbal Pregnancy Screen	X				
PROMIS Global 10- SF	X	X	X $	X	X $
Pain Interference	X	X		X	
Pain Intensity (VAS Score)	X	X #	X %	X #	X
Frequency of Attacks	X	X	X $	X	X $
Rescue Medications		X %	X %	X %	X
Randomization	X				
Clinical Procedures/ Assessments					
Physical Exam (general)	X	X		X	
Physical Exam (pain)	X				
Vitals (HR, RR, Temp, BP)	X	X		X	
Height/ Weight	X				
12-Lead ECG ^	X				
Continuous ECG monitoring		X		X	
Nerve Block Administration		X		X *	
Imaging MRI/ CT report +	X				
Adverse Events		X	X	X	X
Laboratory Procedures					
Urine Pregnancy Test		X		X	
Urine Drug Screen	X				

#: Collected every 30 minutes for 8 hours by text message (REDCap) or patient diary
%: Collected daily for up to 28 days by text message (REDCap) or patient diary
$: Collected weekly for up to 4 weeks by study nurse phone call
*: If pain score >5
+: Review recent imagining, if not available then order as standard of care
^: Order 12-lead ECG as standard of care if one not available within 2 months of screening visit

Study Visit 1: Consent and Screening (Day -15 to Day 0)

Patients with facial pain will be evaluated in clinic; those deemed to have a diagnosis of painful trigeminal neuropathy will be considered for enrollment. Informed consent will be obtained prior to collecting data. Those patients that meet eligibility (inclusion/exclusion criteria outlined above) will be introduced to the study. Consented patients will become enrolled as study participants and will complete baseline measurement prior to randomization. Baseline data that will be collected includes demographics (name, age, sex), physical examination; heart rate and rhythm, blood pressure; comorbid health conditions and prior surgeries or treatments; current and past medications within 6 months. Dr. Edwards will order an EKG if the participant has not had one within the past 2 months prior to the visit, as part of standard care. The targeted pain history will include pain duration, frequency of exacerbations, location, radiation, severity (VAS), quality, instigating event, exacerbations, alleviations, pain treatment frequency and duration of use (non-medical and medical treatments) and changes in pain over time. The targeted pain physical exam will include assessment of light touch test for allodynia and pinprick test for hyperalgesia of the trigeminal dermatome V1-3 regions of the face. Standard practice prior to trigeminal nerve block is to review recent MRI or CT imaging to ensure safety of needle approach to target location. If no recent imaging exists, this will be ordered as part of standard care prior to nerve block. Participants will be asked if there is a possibility they are pregnant. Women of childbearing potential will be educated on birth control methods and will agree to 2 methods of birth control that they will plan to use during the study period (abstinence is an appropriate method). A urine drug screen for illicit use of controlled substances will be obtained. Patient-reported outcome forms to be completed include the PROMIS Global-10 SF and Pain Interference forms. Current and average 24-hour pain (VAS) before procedure will also be recorded. Assessments will be recorded according to the patient's preference, either on paper or via electronic forms using REDCap. All data will be entered into REDCap.

Study Visit 2: Procedure 1 (Day 1)

Participants will be asked to record their pain intensity, 24- hour VAS and current VAS, before the procedure to establish a baseline pain score. Other data will be collected for secondary measures: frequency of pain attacks, basal and breakthrough opioid and non-opioid analgesic frequency and dose. Overall quality of life (PROMIS Global-10 short form) will be assessed.[39] Women of childbearing potential will undergo a urine pregnancy test prior to receiving the nerve block.

<u>*First trigeminal nerve block procedure:*</u> Participant will receive either study drug (guanfacine and lidocaine combination) or active control (lidocaine alone) for the trigeminal nerve block based on randomization. Participants will be monitored for pain intensity at 30-minute time intervals for the first 8 hours after block in addition to safety monitoring procedures. Participant responses will be collected at 30 minute intervals for the first 8 hours while in the recovery (first 60 minutes) and after discharge home, with responses allowed all the way until the next time point and actual time of the response being used in analysis. Assessments will be recorded according to the patient's preference, either on paper or via text message) using the Twilio application linked to REDCap. Patients will also receive a sheet with contact information for the study nurse.

First follow-up period (Day 2 to Day 14)

Participants will be monitored once daily at approximately the same timepoint for 14 days using text message generated using the Twilio application or recorded on a paper diary. Participants will also be monitored for any use of rescue medication (analgesics) once daily. The study nurse will monitor participants once weekly for overall quality of life via phone call using the PROMIS global 10 SF. Participants will be instructed to contact the study nurse with any adverse events directly by phone.

Study Visit 3: Procedure 2 (Day 15-28)

At the end of the first follow-up period, participants will be contacted for crossover to the other arm to receive the second trigeminal nerve block using the alternative drug (study drug or active control), not received during the first nerve block. At the second study visit, participants will record 24-hour VAS and current VAS, and the PROMIS Global-10 Short Form to establish baseline measurement again. Women of childbearing potential will undergo a urine pregnancy test prior to receiving the nerve block.

If VAS < 5 on the pain scale, participants will not be eligible for second trigeminal nerve block during the visit. Study nurse will continue monitoring the participant's pain intensity (daily through day 15, and weekly thereafter) to see if the participant pain is above 5 on the pain scale and eligible for the second block. In general, the study intends that participants would receive both treatments unless they experience intolerable toxicity. If a participant is unable or ineligible to receive second trigeminal nerve block, then the participant's data collected during the first nerve block will be included in the analysis. In addition, a replacement participant will be enrolled so that the minimum number of 30 for each arm is reached. An intention-to-treat analysis will be done post-hoc to evaluate any differential progress to second block between the initial randomized groups.

Second trigeminal nerve block procedure: Participant will receive second trigeminal nerve block followed by monitoring for pain intensity at 30-minute time intervals for the first 8 hours after block, again allowing responses all the way until the next time point.

Second follow-up period (14 days)

Participants will be monitored once daily at the same timepoint for 14 days using text message generated using the Twilio application or recorded on a paper diary. Participants will also be monitored for any use of rescue medication (analgesics) once daily. The study nurse will monitor participants once weekly for overall quality of life via phone call. Participants will be instructed to contact the study nurse with any adverse events directly by phone.

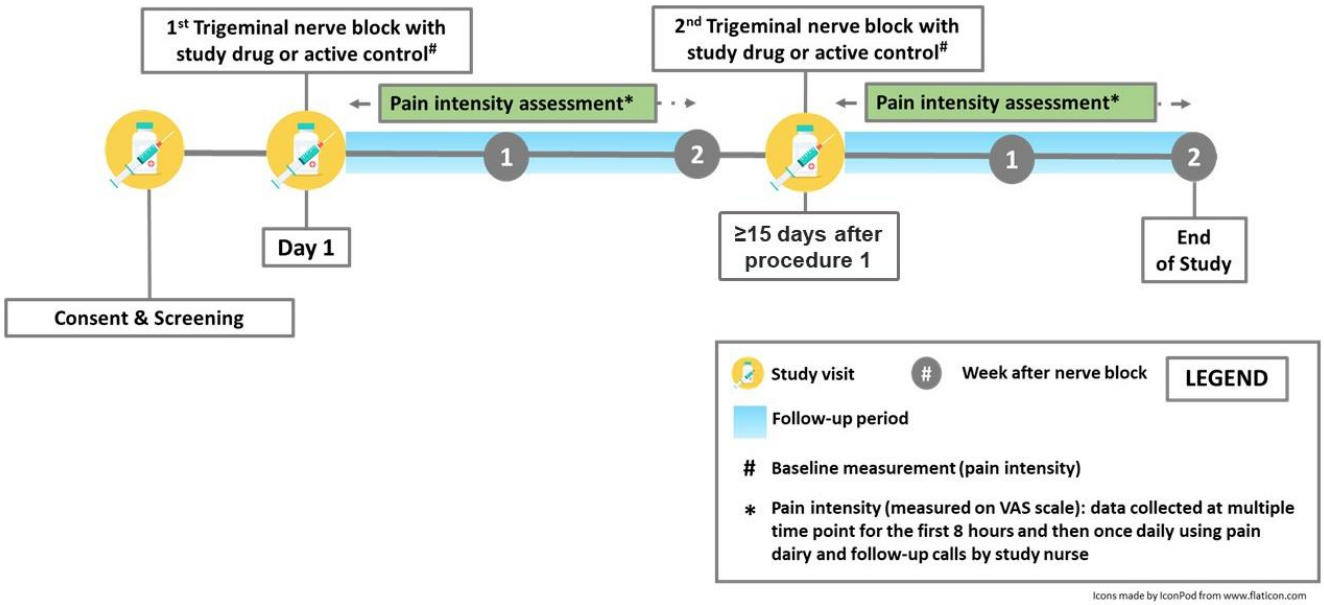

Figure: 1. Study Schema

6.0 RISKS

During the consent process, study personnel will address potential discomfort and risks associated with the protocol. These will be included in the consent form.

Based on the known common side effects of the study drugs and the trigeminal block procedure, the following risk associated with participation in the study are perceived as low:

- Bradycardia
- Hypotension
- Dry Mouth
- Sedation
- Dizziness
- Headache
- Bruising, redness, itching, or swelling at the site of injection
- Intravascular injection resulting in seizure or stroke
- Bleeding
- Increased pain

In the event sedation or dizziness is observed after the procedure, standard of care practices for managing side effects will be performed, and the event will be documented and recorded according to the regulation.

It is understood that there may be as-yet unknown or unanticipated adverse effects of this study treatment. The study team will continually monitor for these effects and consider altering the protocol if needed to ensure patient safety. Changes in the procedures of the study, as well as any change(s) in the risks and/or benefits will be presented to and discussed with the subjects upon approval from the appropriate regulatory bodies for implementation of such revision(s).

Safety Monitoring:

Patients are examined on the day of the procedure to confirm the source of pain, vital signs are stable and in normal range, and female patients are confirmed not-pregnant through point of care pregnancy tests. During the procedure continuous pulse oximetry is used to monitor oxygenation, blood pressure is obtained every 2 minutes, and 3-lead electrocardiogram is monitored for heart rate and rhythm. Following the procedure, patients are taken to the recovery room adjacent to the procedure room to be monitored for 1 hour with continuous pulse oximetry, blood pressure (measured every 5 minutes), and continuous ECG to ensure stable vital signs. The patients are discharged home with a responsible adult after recovery. Before, during, and after the procedure patients are monitored by a registered nurse skilled in the evaluation of vital signs and familiar with the procedure. Dr. Edwards is an Anesthesiologist and will be present for the duration of patient care.

Data Monitoring:

The PI and study coordinator will be responsible for real-time monitoring of all trial-related activities. Dr. Edwards will assure that the study is conducted according to Good Clinical Practice Guidelines and according to FDA requirements. The study team will meet bi-weekly to review recruitment, enrollment, retention, status of each participant currently enrolled, adverse events. Targets will be established for enrollment and completion and reviewed at each meeting where strategies will be discussed to assure that the study is on track. Enrollment tables will be developed by the coordinator and project manager for review at team meetings. Adverse and serious adverse events reports will be monitored in real-time by the PI, project manager, and study coordinator. All final

data will be stored on case report forms in REDCap with all source documents uploaded into REDCap then shredded.

All study data, including those captured from the EHR and other hospital databases, will be transferred into the study database via standardized electronic case report forms (eCRFs) which will reside in a centralized REDCap database located on Vanderbilt's secure servers. REDCap is a secure, web-based application for building and managing online databases. Vanderbilt University, with collaboration from a consortium of institutional partners, including the Vanderbilt Institute for Clinical and Translation Research (VICTR) Informatics Core, developed and manages a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. All study data will be entered via a password protected, study unique REDCap database website. REDCap servers are housed in a local data center at Vanderbilt and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA Security guidelines and is recommended by both the Vanderbilt University Privacy Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports more than 2,700 academic/non-profit consortium partners and over 657,000 research end-users (www.project-redcap.org). Data will be accessed via password protected and secured Web-based interface for data entry and data cleaning. REDCap contains an audit trail for tracking all activities within the system.

To ensure data is accurately and completely collected during the study, periodic monitoring will occur by the Project Manager to ensure the study protocol is being followed, protocol changes have been implemented appropriately, data are being captured per protocol, and are accurate, complete, and current for study subjects. Per best practice guidelines, the monitor will compare a representative number of subject records and other supporting documents with the investigator's reports. Specifically, monitoring activities will include:

[1] A **Technical Review** annually which will consist of the Project Manager examining the quality and accuracy of data, regulatory documents, and other essential documents. Data quality and accuracy will be reviewed through a CRF data and source document review. The Project Manager will randomly select a pre-determined number of study participants to serve as a representative sample. Regulatory Document Review will consist of a review of IRB approvals, informed consents, critical documents, and protocols/amendments.

[2] The **Scientific Review** will occur biennially and will consist of a review of the study's organizational structure, patient recruitment, staff training, and quality control procedures by the Project Manager. Site monitoring progress reports will be submitted to the DSMB and other regulatory bodies (IRB, FDA and NIH) as requested and/or required. This Monitoring Plan will serve as a method for identifying systematic problems and provide a means in which to institute resolution and follow-up and therefore increase data quality.

Any omissions and corrections to data submitted to REDCap are noted and queries are generated by the Project Manager or by REDCap's automated system. Data are checked and verified by the Project Manager. A green check is placed beside items that have been verified as accurate when compared to source documentation. For those items that are not initially verified, a query will be issued using the Data Quality Tool in REDCap. Users will then be able to pull up a list of queries using the Resolve Issues Application. Queries will be responded to directly on each respected eCRF page. Furthermore, there is an option to upload additional documentation if requested by the Project Manager. Once a query has been answered, the Project Manager will review the new information and choose to either re-query the data point or close the query by verifying that the data point is complete and accurate. Once all data points on the eCRF page have been reviewed and verified as accurate, a green verification check will be placed at the bottom of the page and the page will be locked, to show that the data on the page is acceptable and ready to be signed off on by the Principal Investigator. If a data point is revised after it was verified and accepted as accurate by the Project Manager then a red exclamation mark will appear

beside the data point. The Project Manager will be notified via the Data Quality Application and will have the option to issue a new query regarding the change or to verify the new data as accurate and complete. All queries will be stored in REDCap's logging and audit trail so that all data revisions are tracked and permanently recorded in order to verify data accuracy. The audit trail will contain a time stamped record of revisions and data entry within the database. All data points entered for the first two patients enrolled at each site will be thoroughly monitored. Thereafter, specific data points that support the primary and secondary endpoints (ex. Inclusion/Exclusion criteria, informed consent, and randomization strata) will be thoroughly reviewed by a Project Manager. 20% to 100% of all additional data points will then be randomly monitored for accuracy. Queries will be issued no later than one month after completed eCRF pages are reviewed. Review will be expedited in cases of urgent concern. Open queries must be answered within 14 calendar days.

All data entered into the REDCap system must come from an original source. Study coordinators will upload all related source documents and medical records that contain information (including Protected Health Information for verification purposes) used in completing the eCRFs into the secure REDCap system. If original source is given verbally and/or if study procedures were documented outside of the medical record, an original source document must be created (which includes applicable signatures and dates) that provides an accurate account of the information that was exchanged. All applicable study source documentation will be uploaded into REDCap for monitoring purposes then shredded.

7.0 REPORTING OF ADVERSE EVENTS OR UNANTICIPATED PROBLEMS INVOLVING RISK TO PARTICIPANTS OR OTHERS

Adverse Event

An AE is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." An adverse event can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

AEs include any of the following:

- Worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- Subject deterioration due to the primary illness
- Intercurrent illnesses
- Drug interactions
- Events related or possibly related to concomitant medications
- Changes of vital signs, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant

Adverse Drug Reaction

In the pre-approval clinical experience with a new medicinal product or its new usage, particularly as the therapeutic dose(s) may not be established, an adverse drug reaction is defined as:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR).

Unexpected Adverse Drug Reaction

An unexpected ADR is:

An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information, also known as reference safety information. The reference safety information is the package insert of the individual drug.

Serious Adverse Event/Serious Adverse Drug Experience

During clinical investigations, serious AEs may occur, if the event is suspected to be drug-related, the event may be significant enough to lead to important changes in the way the medicinal product is developed (*e.g.*, change in dose, population, needed monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function.

A serious AE (SAE) or serious adverse drug experience (SADE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening. 'Life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E6).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity (as per reporter's opinion)
- Is a congenital anomaly/birth defect
- Is another medically important condition. Important medical conditions that may not result in death, be life-threatening or require hospitalization may be considered as SAEs or SADEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse [Code of Federal Regulations Title 21, Volume 5, 21CFR312.32, revised April 1, 2006].

Please note: Serious is not synonymous with severe. An event may be severe (e.g., severe headache) but still be of minor medical significance. Serious refers to an event that poses a threat to the subject's life or functioning.

Assigning Severity to an Adverse Event

Mild: Causing no limitation of usual activities,
the subject may experience slight discomfort.
Moderate: Causing some limitation of usual activities,
the subject may experience annoying discomfort.
Severe: Causing inability to carry out usual activities;
the subject may experience intolerable discomfort or pain.

Assigning Relationship of Adverse Event to Study Drug (Causality)

The Principal Investigator will determine the relationship of each SAE to study drug (i.e., causality) by using the classification criteria 'not related,' 'possibly related', or 'probably related'. Descriptions of the three classification categories are as follows:

Not Related

Exposure to study drug has not occurred; administration of study drug and the adverse event are not reasonably related in time; or the SAE is considered by the Investigator to be due to a pre-existing condition, a known manifestation of the target disease, a recurrent condition, or is likely explained by environmental or diagnostic therapeutic factors or was pre-existing and did not deteriorate.

Possibly Related

The SAE occurred during or within a reasonable period of time after administration of the study drug, or a pre-existing event worsened within an appropriate period of time after administration of study drug, but the SAE

could be explained equally well by factors or causes other than exposure to the study drug. This category will also be used if there is a lack of information, or insufficient or conflicting evidence exists for classifying the causality of the SAE.

Probably Related
The SAE occurred during or within a reasonable period of time after administration of the study drug or a pre-existing event worsened within an appropriate period of time after administration of study drug, and at least one of the following criteria is applicable:

- the event could not be explained by the clinical condition or history of the subject, environmental or toxic factors, or other diagnostic or therapeutic measures;
- the event was an expected ADR associated with study treatment or a class-labeled drug effect;
- the SAE subsided or disappeared after withdrawal or dose reduction of study treatment; or
- the SAE recurred after re-exposure to study treatment.

Adverse Event Recording
Each adverse event occurring to a subject, either spontaneously revealed by the subject or observed by the Investigator, whether believed to be related or unrelated to the study drug, must be recorded on the AE Case Report Form and the subject's file.

Adverse Event Reporting
All adverse events (AEs) recorded on the adverse event form and will be sent to the Principal Investigator (PI) within 72 hours of the event. AEs will be reported to the IRB according to the IRB policies and procedures. Any unanticipated problems involving risk to the participants or others will be discussed with the Principal Investigator (PI).

Serious Adverse Event Reporting
All SAEs will be recorded on the adverse event case report form and will be reported to the Principal Investigator within 24 hours after becoming aware of their occurrence. All SAEs will be reported to the IRB and FDA in accordance with applicable regulations and policies. Our procedures for reporting the serious adverse events will be as follows: 1. SAEs will be recorded in the patient's study chart and reported to the Principal Investigator within 24 hours of the study team's awareness of the occurrence by email or text message and will be reported to Vanderbilt's IRB according to IRB policies (5 working days). The Study Coordinator will report the event within 5 business days to the Safety Monitor who will be responsible for systematically reviewing SAEs, assigning causality, and evaluating relatedness of each event. The Principal Investigator will have the opportunity to review and agree (or not) with the Safety Monitor's determination on each event. When the Safety Monitor suspects an event is study-related, he/she will have the opportunity (if he/she chooses) to access additional data in order to conduct appropriate safety monitoring. The Safety Monitor will determine if any necessary actions need to occur as result of the event in order to increase the safety of the protocol.

Safety Stopping Criteria:
The trigeminal block procedure is standard of care in the pain clinic. Expected effects of successful block include transient numbness, transient facial weakness including ipsilateral eyelid lag, and rare visual changes all of which resolve with the resolution of the effects of lidocaine over the typical course of 2 hours. Rare risks of the block procedure include infection, bleeding, nerve injury from the mechanical placement of the block needle. Rare risks of using lidocaine during the block procedure include intravascular or subdural injection resulting in transient unresponsiveness and/or seizure, mild sedation, bradycardia, and arrhythmias. These rare risks and side-effects must be differentiated from potential side-effects due to the addition of guanfacine. As all eligible patients are in

clinic for diagnostic nerve block as standard of care, they will receive clinical consent to treatment for the injection procedure itself and necessary x-ray radiation as part of routine care.

Common side-effects of daily oral use of guanfacine include dizziness, drowsiness, tiredness, low blood pressure, and slow heart rate. These side-effects are similar among other medications in the same class including clonidine, dexmedetomidine, tizanidine. Clonidine is also used as an intrathecal analgesic and as a perineural adjunctive injectate for regional blocks. We would expect that the side-effects of guanfacine as an adjunct to lidocaine block might additionally include increased dizziness, drowsiness, tiredness, low blood pressure, and slow heart rate. If the level of sedation experienced by at least 20% of patients in either group is greater than anticipated either by severity or duration, study enrollment will be stopped and the safety monitor engaged for an interim review of data comparing the study groups. If oversedation is occurring in only one group, an adjustment will be made to maintain monitoring for more than an hour (as is standard) until complete recovery.

Potential adverse events (AE) including any occurrence of the above listed procedural or medicine-related side-effects and risks will be documented as AE's, described and categorized as mild-, moderate-, severe- AE and submitted for review by the safety monitor and IRB. The PI will also submit the likelihood of the AE being potentially related to the use of guanfacine. Severe AEs would include the occurrence of a seizure, severe sedation requiring ventilation support; bradycardia, unstable arrhythmias, or hypotension requiring resuscitation (medical or mechanical). The occurrence of a severe AE that is deemed study related would result in a stop of enrollment to report the data to the IRB, and FDA guidance would be obtained prior to study restart.

8.0 STUDY WITHDRAWAL/DISCONTINUATION

Participants will be advised that they have the right to withdraw from the study at any point in time for any reason. During the study, if the participants no longer wants to participate, they will be withdrawn from the study. Contact information for the PI and study staff will be made available to the participant upon enrollment in the consent document.

Subjects will be withdrawn from the study if the PI's medical judgment is that participation places the subject at risk for harm.

9.0 STATISTICAL CONSIDERATIONS

The effects of guanfacine adjuvant (intervention) versus active control on the time to return to baseline pain (primary) will be assessed using linear mixed-effects regression, adjusting for randomization order group and its interaction with the intervention/control indicator. A random intercept indexed by study participant will be used to account for within-participant correlation of the pre- and post-crossover measurements. The linear model assumptions will be assessed by examining residuals, conditional on the empirical Bayes estimates of random effects. If there is evidence that the linear model assumptions are violated (e.g., non-normal residuals or the very unlikely possibility of right censoring), alternative model formulations will be considered as necessary. The overall effect of intervention on the primary outcome will be tested using a two degree-of-freedom chunk test against the null hypothesis of no intervention main effect and no order-by-intervention interaction. The effects of intervention on the mean time to return to baseline will be summarized using estimates and 95% confidence intervals, stratified by order group. The effects of guanfacine adjuvant versus active control on secondary outcomes will be assessed using similar mixed-effects regression techniques as appropriate for the type of outcome (including proportional hazards, cumulative logit, logistic, and linear regression methods), adjusting for

randomization order group and its interaction with the intervention/control indicator. A random intercept indexed by study participant will be used to account for within-participant correlation. Quantitative and/or graphical regression diagnostics will be examined, and alternative model formulations will be considered as appropriate. Intervention effects will be tested and summarized as described above. No familywise hypotheses will be tested; no adjustments will be made to control any familywise type-I error probability. The type-I error rate will be fixed at 5%. All statistical analyses will be implemented in R (www.r-project.org; latest version) and the add-on package "lme4" and other packages as necessary.

9.1 Statistical power and sample size. Evidence from the medical literature and expert opinion suggests that the mean duration of pain relief after treatment with lidocaine alone (active control group) is approximately 140 minutes. The sample size for the proposed study was selected to achieve at least 80% power to detect a 20% or greater increase in the duration of pain relief after treatment with lidocaine plus guanfacine as an adjuvant (treatment group). This corresponds to a mean difference of 28 minutes. Again, although this degree of difference is not likely to be clinically meaningful, we are conducting this trial as a proof of mechanism only. If successful, we would pursue a modified formulation of guanfacine such that delivery was extended and pain relief duration was considerably longer. A simulation-based power analysis was implemented using linear mixed-effects regression as described above. Both between- and within-subjects variability were conservatively assumed to have standard deviation 30 minutes. Under these conditions, 30 participants will ensure approximately 90% power to detect a significant mean difference (28 minutes or greater in pain relief duration). **Figure 2** illustrates the estimated statistical power for somewhat larger and smaller effect sizes (i.e., 15%, 20%, and 25% increase in pain relief duration), for a variety of sample sizes.

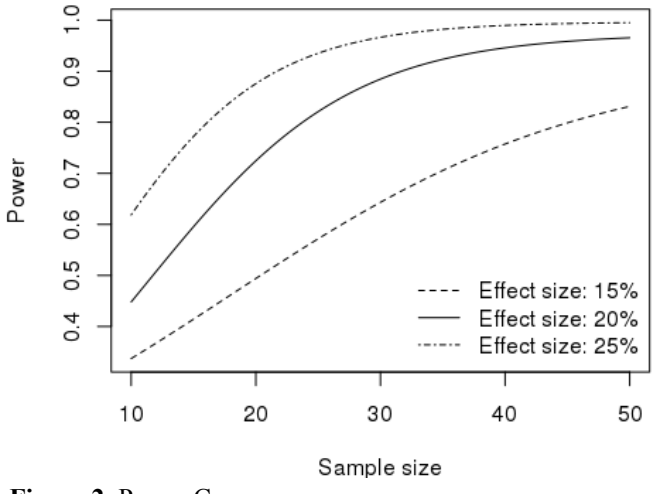

Figure 2. Power Curves

Dropout and intent-to-treat: If VAS < 5 on the pain scale, participants will not be eligible for second trigeminal nerve block during the visit. Study nurse will continue monitoring the participant's pain intensity daily (days 15-28) to monitor when the participant pain is above 5 on the pain scale and eligible for the second block. In general, the study intends that participants would receive both treatments unless they experience intolerable toxicity. If a participant is unable or ineligible to receive second trigeminal nerve block, then the participant's data collected during the first nerve block will be included in the final analysis. In addition, a replacement participant will be enrolled so that the minimum number of 30 for each arm is reached. An exploratory analysis will be done post-hoc to evaluate any differential progress to second block between the initial randomized groups. Approximately 70 people with painful trigeminal neuropathy will be evaluated at Vanderbilt University Medical Center to determine if they are eligible to take part in this study. We expect to consent 70 subjects with 30 completing the full study.

Although 28-70 incremental/additional minutes of pain relief would be clinically significant by itself, the study finding would validate the pain relief mechanism of guanfacine in the trigeminal nerve and show that enhanced pain relief can be achieved by the combination of drugs, and therefore extends the utility of the mechanism into further clinical development.

10.0 PRIVACY/CONFIDENTIALITY ISSUES

A database will be designed for this study using REDCap (Research Electronic Data Capture) tools. REDCap is a secure, web-based application designed to support data capture for research studies and was developed specifically around HIPAA-Security guidelines. PI and study personnel are trained in HIPAA privacy regulations. All reasonable efforts will be made to keep a patient's protected health information (PHI) private and confidential. Participants will be identified with a study identification number. There will be limited access to medical records and de-identification of all records. Federal privacy guidelines will be followed when using or sharing any protected health information.

Much like email, text messaging is not considered a secure form of communication. These surveys use a third-party service called Twilio to deliver the text messages and collect your answers. REDCap goes to great lengths to ensure that text transcripts do not stay in Twilio's records but are removed shortly after being completed and transferred to REDCap. This is done for privacy and security concerns –answers and phone number do not get permanently logged in Twilio's computers but instead remain securely in REDCap.

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APPENDIX A: FORMULATION INSTRUCTIONS FOR GUANFACINE 250 MCG IN LIDOCAINE 1% PF 6 ML FOR INJECTION (GUANFACINE HYDROCHLORIDE AND LIDOCAINE 1%, INJECTION)

Final Product: Guanfacine hydrochloride 250 mcg in lidocaine 1% PF 6 mL
Final Concentration: 41.67 mcg/mL

Supplied: Guanfacine hydrochloride powder (Procos S.p.A.)

Storage: 72 hours refrigerated

Dispensing: Dispense in a 10 mL syringe with tamper evident leur cap

Supplies: Guanfacine hydrochloride powder
Lidocaine 1% PF 30 mL vial
Weight boat
5 mL, 10 mL, and 60 mL sterile syringes
0.22 micron disk filter

***MIXING INSTRUCTIONS*:**

1. Compounding area is clean, sanitized, and free of components and/or residue of other compounding procedures and the compounder is wearing appropriate PPE.
2. Tare weight boat and print. Weigh 0.03 g of guanfacine hydrochloride powder and print.
3. Draw up 24 mL Sterile Water (SWFI) and add to weighted guanfacine hydrochloride powder to make aliquot (30,000 mcg/24 mL).
4. Draw up 1 mL of guanfacine aliquot (1250 mcg/mL).
5. Draw up 29 mL of Lidocaine 1%.
6. Allow pharmacist(s) to check ingredients (compounding verification)
7. Pull plunger from a 60 mL syringe and add a tip cap.
8. Add 29 mL of Lidocaine 1% to barrel.
9. Add 1 mL of guanfacine aliquot (1250 mcg/mL) to barrel.
10. Replace plunger and attach a 0.22 micron disc filter and leur to leur adapter to filter 6 mL of solution into the final 10 mL syringe.
11. Add a tamper evident leur cap.
12. Perform filter integrity test and bubble test on the filter.
13. Filter integrity test _____PSI Bubble Test _____ PSI (PASS/FAIL)
    a. The minimum bubble point is 46 psi for this filter unit. Presence of bubbles at less than 46 psi represents a filter failure and the compounding process must be aborted.
    b. A successful bubble point test coupled with the satisfactory testing results (sterile per USP<71>) on the representative process verification sample performed prior to opening the study serve as criteria for release of the dose.
14. The compounding area is clean and sanitized and free of components and/or residue of this preparation.
15. Final verification and quality assurance check by:

Pharmacist: _____ Date:_____ Time:_____

a. Rx Label syringe with a 72 hour expiration refrigerated per USP 797.
b. The compounded preparation label has been affixed to the final container
c. High alert sticker has been affixed to final container
d. "Medication is sterile, Packaging is not" has been affixed to the final container
e. No particles observed
f. Final weight and volume of preparation has been verified
g. Preparation dispensed in an appropriate container
h. Container is not contaminated by drug

FORMULATION INSTRUCTIONS FOR LIDOCAINE 1% PF 6 ML FOR INJECTION (LIDOCAINE 1%, INJECTION)

Final Product: Lidocaine 1% PF 6 mL

Supplied: n/a

Storage: 72 hours refrigerated

Dispensing: Dispense in a 10 mL syringe with tamper evident leur cap

Supplies: Lidocaine 1% PF 30 mL vial
10 mL and 30 mL sterile syringes
0.22 micron disk filter

***MIXING INSTRUCTIONS*:**

1. Compounding area is clean, sanitized, and free of components and/or residue of other compounding procedures and the compounder is wearing appropriate PPE.
2. Draw up 10 mL of Lidocaine 1%.
3. Allow pharmacist(s) to check ingredients (compounding verification)
4. Add Lidocaine 1% to a clean 30 mL syringe.
5. Attach a 0.22 micron disc filter and leur to leur adapter to filter 6 mL of solution into the final 10 mL syringe.
6. Add a tamper evident leur cap.
7. Perform filter integrity test and bubble test on the filter.
8. Filter integrity test _____PSI Bubble Test _____ PSI (PASS/FAIL)
    a. The minimum bubble point is 46 psi for this filter unit. Presence of bubbles at less than 46 psi represents a filter failure and the compounding process must be aborted.
    b. A successful bubble point test coupled with the satisfactory testing results (sterile per USP<71>) on the representative process verification sample performed prior to opening the study serve as criteria for release of the dose.
9. The compounding area is clean and sanitized and free of components and/or residue of this preparation.
10. Final verification and quality assurance check by:

Pharmacist: _____ Date:_____ Time:_____

a. Rx Label syringe with a 72 hour expiration refrigerated per USP 797.
b. The compounded preparation label has been affixed to the final container
c. High alert sticker has been affixed to final container
d. “Medication is sterile, Packaging is not” has been affixed to the final container
e. No particles observed
f. Final weight and volume of preparation has been verified
g. Preparation dispensed in an appropriate container
h. Container is not contaminated by drug