Study Protocol

Official Title: Device assisted exercises for improving soft palate and Eustachian tube function in children between ages 6-17 with or without cleft palate and with ventilation tubes

ClinicalTrials.gov ID (NCT number): NCT03868891

IRB ID: PRO18110061 / STUDY19110160

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Scientific Background

For optimal hearing, i.e., sound transmission from the tympanic membrane to the inner ear, the middle ear (ME) needs to be free of effusion and maintain near-ambient pressure. The gas partial pressure differential between the normally air-filled ME and the ME mucosa creates a diffusion gradient towards blood that results in a progressive decrease in middle ear pressure (MEP). At a critical pressure of ≈-300 daPa (ref. ambient), the ME mucosal (MEM) capillaries dilate and leak, with transudation of fluid into the ME cavity and mucosal inflammation, termed OME. Under normal physiological conditions, OME is prevented by muscle-assisted, intermittent opening of the usually closed Eustachian tube (ET), which allows the exchange of a gas bolus between the nasopharynx (NP) and ME to restore near-ambient MEP. Data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 2005 to 2012 estimate that ETD and OME affect 40% and 53% of the population, respectively (adults and children combined), and are responsible for more than 2 million related medical visits each year. Because no medical therapy is efficacious in improving ETF, the disease is usually managed by surgical insertion of a VT into the tympanic membrane of the affected ear(s). Mechanistically, a VT bypasses the ET to preserve ME-ambient pressure equivalence, clears extant ME effusion and resolves MEM inflammation. However, with constitutively poor ETF, the disease often recurs after the VT is displaced or blocked, and repeated VT insertions are required to preserve ME health.

Previous studies performed in our laboratory have identified functional variables and examined their effects on ET opening in subjects without CP [1-4]. There, specifically, frame-by-frame image analysis of NP video endoscopy recorded during swallows has demonstrated that 1) higher soft palate elevation, 2) longer duration of soft palate elevation and delay in relaxation, 3) larger rotation of the ET posterior lamina secondary to soft palate elevation and 4) a wider angle between the posterior and anterior laminas are associated with more effective ET opening and improved ME pressure (MEP) equilibration. These observations imply that soft palate elevation and levator veli palatini muscle (mLVP) contraction may have a more important role than previously thought. The association between ETD and VPI secondary to submucous cleft or cleft palate, even after surgical repair, is well known [5,6]. These studies support persistent need for tubes long after palatoplasty. In addition, a correlation between VPI and persistent ETD was demonstrated by a study conducted by the PI [5]. We propose that non-CP subjects with a history of OM demonstrate abnormal weak VP closure with similarities to post-palatoplasty CP subjects.

Here we hypothesize that children older than 5 years with or without CP with ongoing need for ventilation tubes (VT) for treatment of OME and TM-R/RP have ETD related to the mechanisms and effectiveness in elevating the soft palate during speech and swallowing. Therefore, modifying and enhancing soft palate elevation may improve ETF. Exercises are very effective in swallowing rehabilitation programs as they induce neural adaptations that result in enhanced synchronization of motor units, improved inter- and intra-muscle coordination, increased central nervous system activation and more efficient neural receptor patterns [7].

We chose a device that is commercially available and easy to use to assist in the practice of exercises targeted to enhance soft palate closure, oral and pharyngeal muscle coordination and strength: the Expiratory Muscle Strength Trainer 150 (EMST150) (Aspire Products LLC,

Atlanta, GA). The EMST150 is a breathing training device used to improve the force and endurance of breathing, voice, swallow and cough. Studies show that it enhances muscle activity during the voluntary and involuntary phases of swallowing, improving VP closing pressure [8] and the contraction of the orbicularis oris, buccinator, suprahyoid and submental muscles [9-10]. We expect the device will promote a sustained mLVP contraction and tight velum closure to prevent air leakage during increased oral pressure.

A gap exists in our knowledge of the relationship between dysfunctional soft palate elevation and ETF, association of patterns of velopharyngeal closure and ETD, and the possibility of improving ETF using therapeutic exercises in patients who suffer from ETD and need VT insertion after age 5.

Expected outcomes of this study include demonstrating the associations between ETD and the anatomical and functional palatal anomalies, providing preliminary evidence for a new ETD treatment modality and the knowledge and documentation to support a future larger clinical trial.

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7. Silverman, E.P., et al., *Tutorial on maximum inspiratory and expiratory mouth pressures in individuals with idiopathic Parkinson disease (IPD) and the preliminary results of an expiratory muscle strength training program.* NeuroRehabilitation, 2006. 21(1): p. 71-9.
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Study Objectives

Our long-term goal is to demonstrate the prevalence of Eustachian tube dysfunction (ETD) and soft palate/swallowing dysfunction in children with (after palatoplasty) and without cleft palate (CP) who continue to need ventilation tubes (VT) for the treatment otitis media with effusion (OME) or tympanic membrane retraction/retraction pocket (TM-R/RP) after age 5, and conduct a trial to test the effect of swallow strengthening exercises for improving ET function (ETF), thereby providing a non-surgical treatment alternative to VT insertion. The short-term goals of this application are to collect data regarding the feasibility, potential problems and limitations, necessary protocol modifications, and data for the sample size calculation for the planned grant application for a larger clinical trial.

Specific Aim 1) Characterize ETD and soft palate dysfunction in children between ages 6-17 with and without CP, who continue to need VTs. We will test the hypotheses that 1a) children with or without CP who continue to need VT have ETD; 1b) a higher proportion of the CP patients have weak and incomplete soft palate elevation and velopharyngeal insufficiency (VPI) during swallowing compared to the non-CP population; 1c) soft palate and ET dysfunction patterns are similar in these CP and non-CP populations with VTs. The experimental approach will include: i) assessment of passive and active properties of the ET with the Forced Response Test and Inflation-Deflation Test; ii) assessment of soft palate closure strength and pattern with the nasal pressure curves on ETF tests; iii) documentation of soft palate closure patterns with videoendoscopy and examination of the oral cavity as the soft palate elevates with phonation and with gag; and iv) for the impact of soft palate closure on speech, perceptual speech evaluation using the Pittsburgh Weighted Speech Score (PWSS). The significance of this study is that it assesses the viability of a new hypothesis for the pathophysiology of ETD.

Specific Aim 2) Evaluate the effects of soft palate muscle strengthening exercises on velopharyngeal closure and ETF in this population with active muscular ETD. We will test the hypotheses that device - assisted exercises using the EMST150 device, will: 2a) improve soft palate function; 2b) improve ETF; 2c) show similar improvements in VP closure and ETF in children with and without CP; 2d) show good subject compliance in using this device. The significance of this aim is to introduce a new underlying mechanism, method of evaluation and treatment modality for ETD. The experimental approach will include repeated evaluation before and after exercises for two months.

Study Design & Methods

Design: Experimental, open label, pre/post

Methods:

Introduction on COVID-19:

This initial introduction summarizes the precautions we have implemented in our lab and the modifications to the research activities to assure the safety of the participants and the safety of the study staff while still maintaining the study goals during the ongoing COVID-19 pandemic.

In compliance with the University of Pittsburgh requirements, the following COVID-19 safety measures were implemented in the MEPL/CHP main:
1) We have elected a Pandemic Safety Officer, acquired PPEs and disinfecting supplies from the Dietrich School Stockroom and have the staff completed the COVID-19 training;
2) We have a Mitigation Plan approved by the Otolaryngology Department and the University of Pittsburgh;
3) Signage for the use of masks and safety distancing have been posted around the lab. Our testing facilities are located in Children's Hospital of Pittsburgh buildings and all staff, patients and visitors go through the standard COVID-19 screening upon entering the building.

Modifications to the research activities:

1) We are reducing the cohort from 3 to 1, therefore from now on all children will perform the exercises with only the EMST-150 device;
2) We are eliminating the nasal endoscopy from all visits to reduce the possibility of contact with nasal and oral fluids. Consequently, pregnancy test becomes unnecessary from now on;
3) To reduce the time spent at our lab for testing, we:
a) Will offer the possibility to talk to the study physician via video-conference (such as Zoom or Teams) to learn about the study prior to coming to the MEPL/CHP main for the screening visit. If they are interested and also sign the Consent form electronically (the new consent form follows the IRB guidelines for electronic consenting), we will also collect the child's medical history at this virtual encounter;
b) Will not perform the Sonotubometry and the VCT tests;
c) Have simplified the nasopharyngeal maneuvers and video-otoscopy evaluations;
d) Will not perform tests on ears with an intact tympanic membrane, unless this is the study ear in which the tympanic membrane has healed after the VT was extruded.
4) Some parts of the tests will be performed only "if" and "when" considered safe. This decision will be based on the risks of exposure to the COVID-19 virus and will take into consideration the status of the pandemic and the possibility to sanitize or adapt filters to parts of the equipment.

COVID-19 testing: as per now, there are no formal recommendations to perform COVID-19 testing prior to an on-site visit. Nevertheless, if in the lifetime of this study there are changes in the course of the COVID-19 pandemic and tests become recommended or mandatory, we will abide to the requirements of the CHP hospital, University of Pittsburgh, state and federal agencies and request that participants are tested for COVID-19 either by nasal swabs or blood tests prior to the on-site visit.

Modified Research Activities:

Following informed consent, at the enrollment visit at the MEPL/CHP main (Visit 1), general medical history and questions specifically related to middle ear (ME) disease and Eustachian tube dysfunction will be asked, the ETDQ-7 questionnaire will be filled out by the subject and/or the parent, and subjects and/or parents of subjects 8 years and older will complete the VELO instrument (a quality of life instrument asking about speech limitations, swallowing problems, situational difficulties, emotional impacts, perception by others, and caregiver impact associated with velopharyngeal insufficiency). We will offer the possibility to talk to the study physician via video-conference (such as Zoom or Teams) to learn about the study prior to coming to the MEPL/CHP main for the initial screening visit. If they are interested and also sign the Consent form electronically, we will also collect the child's medical history at this virtual encounter.

At the screening visit in the lab, a general and Ears Nose and Throat (ENT) physical examination will be performed and height, weight, blood pressure and pulse will be recorded. A tympanogram will be obtained to confirm the presence of at least one non-intact tympanic membrane and, if the subject qualifies to proceed, study-specific examinations and testing will be performed. They will include baseline Eustachian tube function (ETF) tests that are applicable to the condition of the ear, i.e. perforation/functional VT (see Study Flow Chart and ETF tests).

Subjects who have normal ETF or have patulous ETF based on the test results will be ineligible to continue in the study. The target ET dysfunction (ETD) phenotype for this pilot trial is patients who have active muscular insufficiency in opening the ET lumen resulting in inability to equalize middle ear (ME) pressure, which will be assessed by the percentage pressure equilibrated (PPEq) obtained during the ETF tests. Specifically, the subject will be considered eligible if his/her PPEq is < 40% after 1 swallow or < 80% after 5 swallows on the Inflation test and/or < 20% after 1 swallow or < 60% after 5 swallows on the Deflation test. In case of bilateral non-intact tympanic membranes, both ears that qualify based on PPEq will be analyzed in the study.

Also at the enrollment visit, subjects will undergo video analysis of soft palate elevation and read/repeat a speech sample that will be video and audio-recorded for later analysis by a speech language pathologist. Subjects will then be trained in the use of the EMST-150 device, and sent home with an instruction handout and exercise diary to track compliance: (pictures of the device appear in consent form) EMST-150 assisted exercises: this marketed device for strengthening respiratory muscles consists of a handheld plastic tube with a mouthpiece on one end and a valve on the opposite end that can be set to vary expiratory flow resistance between 30 cmH2O to 150 cmH2O pressure. The subject takes a deep breath, seals the lips around the mouthpiece and breathes out against resistance for as long as possible. To achieve the purpose of this study, strengthening the velum, the EMST-150 will be deployed without the nose clip, forcing velopharyngeal (VP) closure to impound air. To establish the initial setting for the home exercises, participants will blow the EMST-150 while oral pressures are recorded (detailed description below). Starting at 30 cmH2O, flow resistance will be gradually increased until airflow is interrupted. The highest resistance at which the participant can blow will be the initial exercise target. Participants will be instructed to perform 5 sets of 5 resistive expirations once a day in a sitting position (due to the possibility of lightheadedness) with a 10-15 second rest between each repetition and a 1-2 minute rest between each set of 5 repetitions. After the first

week of training, the control knob will be turned one quarter to increase expiratory resistance, always ensuring that air can still move through the device. During the subsequent 7–11 weeks (depending on when Visit 2 can be scheduled), the same procedure (increasing exercise target) will be performed. Participants will take a picture with their phone of the EMST setting each week and will have a diary in which to log the completion of exercises. Each session should take approximately 10-15 minutes, for a total of 10-15 minutes per day.

The weekly pictures of diaries will be saved by participants/parents on their phones. If the participant loses the paper copy of the diary, then they may send the picture(s) of the completed diary to the research staff via email. The pictures of EMST settings will be looked at during the post-exercise (Visit 2) study visit; they will not need to be sent or printed.

Research staff will interact by phone/email with participants weekly in non-visit weeks to provide logistical support and motivation to continue the exercise protocol. The subjects will be brought to the MEPL/CHP main for tests and clinical re-evaluation to assess the change in muscle strength and ETF after 2–3 months of continued exercise (Visit 2). The devices and exercise diaries will then be collected, and pictures of home EMST-150 settings will be viewed by the study team.

Assessment and procedures performed at the MEPL/CHP main:

At the MEPL/CHP main we will use a series of tests to characterize the active and passive properties of the ET:

1. Forced Response Test (FRT): The FRT requires a non-intact tympanic membrane and uses an instrument developed in our laboratory consisting of an ear canal probe coupled serially to a differential pressure transducer, via a valve to a flow sensor and via a second valve to a variable-speed constant-flow pump. The probe is sealed in the test ear canal and both valves are opened. The pump is set to deliver a constant flow of approximately 11 ml/min which increases ME pressure to passively open the ET (PO). This is followed by a decrease in ME pressure to steady state pressure (PS) and flow (QS) conditions. The subject is asked to swallow which either transiently increases (further ET dilation) or decreases (ET constriction) the trans-ET flow (QA). The pump is turned off causing the ET to close at a residual ME pressure (PC). This procedure is repeated at flow rates of approximately 23 ml/min. High opening (PO >500 daPa) and closing (CP > 120 daPa) pressures indicate extrinsic or intrinsic ET obstruction and low opening (PO < 200 daPa) and closing (CP < 30 daPa) pressures may indicate a patulous or semi-patulous ET. Passive resistance (RO=PS/QS) is a measure of ET luminal compliance, active resistance (RA=PA/QA) is a measure of the change in the ET luminal compliance with swallowing and dilatory efficiency (DE=RO/RA) is a standardized measure of muscle-assisted ET opening efficiency independent of luminal adhesive forces.

2. Inflation-Deflation Test (IDT): The IDT requires a non-intact tympanic membrane and uses the FRT instrument. ME pressure is increased to approximately 200 daPa (ref ambient), the valves to the flow sensor and pump are closed and the subject is asked to swallow repeatedly at a natural interval while monitoring ME pressure until further swallowing fails to change ME pressure. The procedure is repeated with an applied under-pressure of approximately -200 daPa.

The test measures the muscle-assisted tubal openings under minor stress (ME under-pressure) and facilitative (ME over-pressure) conditions and can detect a patulous/semi-patulous ET by an inability to maintain applied ME over- and/or under-pressures between swallows. The outcome variable is the PPEq at each swallow.

3. Pressure Chamber ET Test: For all ears with healed tympanic membranes in case of VT extrusion after the enrollment in the study, the PPEq will be assessed with a hypo/hyperbaric pressure chamber and a tympanometer. The subject and a technician enter the chamber and chamber pressure is increased to a pressure sufficient (approximately 150 to 300 daPa) to create a relative ME under-pressure of approximately -200 daPa which is confirmed by tympanometry. The individual performs a series of 5 swallows and the relative ME pressure is measured after the first and fifth swallows. Then the chamber pressure is decreased to a pressure sufficient to create a relative ME over-pressure of approximately 200 daPa confirmed by tympanometry. The individual performs a series of swallows and the relative ME pressure is measured after the first and fifth swallows. The outcome variables are the PPEq at positive and negative ME pressure. Then the chamber pressure will be decreased at a constant rate towards -1000 daPa to elicit spontaneous openings of both ETs. At the same time, a small nasal probe with a speaker will be placed at one of the nostrils to deliver a high pitch sound and earplugs with embedded microphones will be placed in the external ear canals to monitor and detect the ET openings. The ME-ambient pressure gradient at the time of ET opening is recorded as the opening pressure and the gradient at the time of ET closure is recorded as the closing pressure. If the Pressure Chamber test is considered unsafe to be performed due to the COVID-19 pandemic, PPEq will be calculate from other tests. The PC test is only available for tests done at the MEPL.

4. Patulous test: The Patulous test detects if there are concurrent changes in the EC pressures during breathing. An ear probe attached to a pressure sensor is sealed in the EC and a nasal olive attached to a pressure sensor is applied to the contralateral nostril. The participant is instructed to breath with increasing intensity (volume) through the same nostril. The same test sequence is repeated on the contralateral side.

5. Nasopharyngeal maneuver: Valsalva and Politzer maneuvers can be done in intact and non-intact TMs. A nasal olive attached to a pressure sensor is applied to one of the nostrils to measure NP pressure variations during the maneuvers and ear plugs are used to detect changes in ME pressure. In case the tympanic membrane is healed and is intact, changes in ME pressure will be also measured by tympanogram. The goal is to measure variations in NP and ME pressures during the maneuver and any residual ME pressure:
a) Valsalva maneuver: The nostril contralateral to the nasal probe is blocked with the finger and the participant is instructed to forcibly blow against the closed nose until achieving a threshold NP pressure around 400 daPa. Failure to increase ME pressure during the Valsalva test is interpreted as a high resistance to ET dilation.
b) Politzer maneuver: We will use a handheld pump device (Eustachi or EarPopper) with a pressure sensor connected to the nose piece to blow a gentle air into the nostril. The contralateral nostril is blocked and the subject is asked to hold their breath, swallow, and maybe blow the EMST (cooperative children) while changes in the nasal and ear pressures are recorded.

6. Tubomanometry: The tubomanometer consists of a pump connected to nasal and ear probes. The ear probe is sealed to the external ear canal and the nasal probe is introduced into both nostrils to deliver a controlled airflow. The subject is then asked to swallow and blow the EMST-150 at low resistance, triggering VP closure and increasing the NP pressure. ET openings are detected as a change in ME pressure measured directly as a pressure pulse in the ear canal for ears with a non-intact TM, or indirectly, caused by TM displacement in ears with intact TMs - an alternative will be to use tympanograms to measure those changes. The test is done at pressure settings of 30, 40 and 50 mbars and the outcome measure is the detection of ET openings. Tubomanometry nasal pressure curves will be used as one of the outcome measure of VP competency. Variables will be: the maximum pressure achieved at the C2 point with respect to the delivered pressure (% Max-achieved), duration of closure of the velum (time between C2 and C3), pressure decay (difference in pressure amplitude between C2 and C3) and area under the C1-C2-C3-C4 curve (as the overall success in keeping the velum closed). The EMST-150 part of this protocol will not be performed if considered unsafe due to the COVID-19 pandemic.

7. Video-otoscopy: it will be performed in all cooperative children. The participant is placed in a sitting position and TM status is recorded using a fiber-optic otoscope attached to a camera. If the TM is intact, pneumatic otoscopy is recorded. The subject may also be asked to swallow, perform the Valsalva maneuver or breath at different intensities to see the effects on TM movement and if necessary to confirm findings of the ETF tests, such as low protection or patulous ET. Throughout, signals from the video camera are continuously and simultaneously recorded via an ADI Octal Bio Amp Power Lab 8/30 and displayed and analyzed using Lab Chart software.

8. Swallow Evaluation (Video-recording of soft palate elevation): Soft palate movement during speech and when activated by a gag reflex will be audio- and video-recorded with the use of an endoscope or an iPad.

9. EMST-150 baseline settings: The EMST-150 will be connected to a pressure sensor and the participant will blow at gradual increments of resistance to establish the ideal settings for the home exercises. Ear plugs or tympanograms (in case the tympanic membrane healed) may be used to detect changes in ME pressure. Maximal flow resistance at which the person can exhale through the device will be chosen as the initial exercise setting. Fewer EMST-150 measurements will be performed if considered unsafe due to the COVID-19 pandemic.

10. Tympanometry: The tympanometer is a handheld instrument used to measure relative ME pressure. The test is simple and requires only that a probe be placed in the external ear canal for a few seconds. The probe introduces a sound and varies the pressure to move the tympanic membrane inward and outward and continuously records the reflected sound. ME pressure is assigned as the applied pressure at which the reflected sound is at a minimum. In case of non-intact tympanic membrane (perforation or tubes), only a measure of volume is obtained.

11. Speech Evaluation: A speech sample will be read/repeated by participants in accordance with the standard protocol for assigning a Pittsburgh Weighed Speech Score (PWSS). The PWSS is a validated measure of speech and VP dysfunction that rates 5 components of speech: nasality, nasal emission, facial grimace, phonatory characteristics and compensatory misarticulations. A

lower PWSS denotes better speech than a higher PWSS. The speech sample will be video and audio recorded at each visit and will be viewed at a later time by a speech language pathologist with expertise working with children with craniofacial disorders, who will assign the PWSS score.

In addition to or instead of the PWSS, speech samples may be assessed using The Cleft Audit Protocol for Speech—Augmented (CAPS-A) (Chapman et al., 2016). A speech-language pathologist who is also a listed co-investigator on this study will rate participants on hypernasality, hyponasality, other resonance distortions, audible nasal emission/turbulence, inaudible nasal emission, voice, speech acceptability, language skills, and fluency.

Eligibility Criteria

Inclusion:
-- Otherwise healthy
-- Currently have unilateral or bilateral ventilation tube(s) (VTs) inserted for otitis media with effusion (OME) or tympanic membrane retraction/retraction pocket (TM-R/RP) or a TM perforation after extrusion of a VT
-- History of at least 2 sets of VT insertions in the past
-- Eustachian tube (ET) function (ETF) tests showing an active muscular pattern of Eustachian tube dysfunction
-- Some degree of velopharyngeal dysfunction during the ETF tests
-- CP cohort: non-syndromic; prior palatoplasty without complications or need for revision
-- Non-CP cohort: have had prior adenoidectomy

Exclusion:
-- Concurrent or past diagnosis of cancer or history of radiation
-- Have or had vestibular pathology, cranial base surgery or ossicular chain reconstruction
-- Craniofacial dysmorphology (other than non-syndromic CP with or without cleft lip in the CP cohort) or other syndrome
-- A non-patent nasal cavity
-- Patulous ET or pathologically low ET opening or closing pressures
-- Unable or unwilling to perform the tests and exercises outlined in the study

Statistical Analysis Plan

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Study Objectives

Specific Aim 1) Characterize ETD and soft palate dysfunction in children between ages 6-17 with and without CP, who continue to need VTs.

Specific Aim 2) Evaluate the effects of soft palate muscle strengthening exercises on velopharyngeal closure and ETF in this population with active muscular ETD.

Study Outcomes

Primary Outcome

- percent of the pressures equilibrated by swallowing on ETF testing

Secondary Outcomes

- plateau decay and percent of the applied pressure on tubomanometry
- change in other ETF measures
- changes in speech evaluation parameters.

Sample Size Calculation

This is a pilot study. Up to 200 subjects with and without cleft palate will be screened to have 30 total subjects (15 with and 15 without cleft palate).

Analyses

Stata/SE version 16.1 will be used for all statistical analysis.
P value < .05 will be used for statistical significance.

Primary Outcome

The primary outcome measure 'percent of the pressures equilibrated by swallowing on ETF testing' will be analyzed with paired t-tests or Wilcoxon signed-rank test depending on the normality of the data. Mean and standard deviations will be reported for normally distributed data and median and interquartile range will be reported for non-normally distributed data.

Secondary Outcome

The secondary outcome measures 'plateau decay and percent of the applied pressure on tubomanometry,' 'change in other ETF measures,' and 'changes in speech evaluation parameters' will be evaluated with McNemar's chi-squared tests for categorical outcomes and paired t-tests or Wilcoxon signed-rank test for continuous data depending on the normality of the outcomes. Frequency and percentages will be reported for categorical outcomes. For continuous data, mean and standard deviations will be reported for normally distributed data and median and interquartile range will be reported for non-normally distributed data.

Cross-Over
Not applicable

Analysis Inclusion
Only those who completed visit 2 will be included in the final analysis.

Missing Data
Data imputation will not be used for missing data.

Harms

Serious adverse events and adverse events will be collected until completion of the participant's last study visit, for a maximum of 8 months following visit 1.