Study Title: Directed topical drug delivery for treatment for PASC hyposmia

Study Product: Beclomethasone; Vectra F-microsponge ; PosiSep microsponge

Protocol Number: **TBD**

NCT ID: **NCT05970731**

Principal Investigator: **Bradley J. Goldstein, MD, PhD**

Sponsor: **Investigator initiated study**

Funded by: **Internal, Duke Head and Neck Surgery**

Version Number: **v.1.2, 16October2023**

All versions should have a version number and a date. Use the international date format (day month year) and write out the month (e.g., 23 June 2015).

_____ _____

Sponsor – Investigator Date

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
	Study Timeline Extended	**Rationale – We prefer to perform the final smell test at a 3 month interval, as ongoing recovery for post-viral smell loss may take several months in many cases.**

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

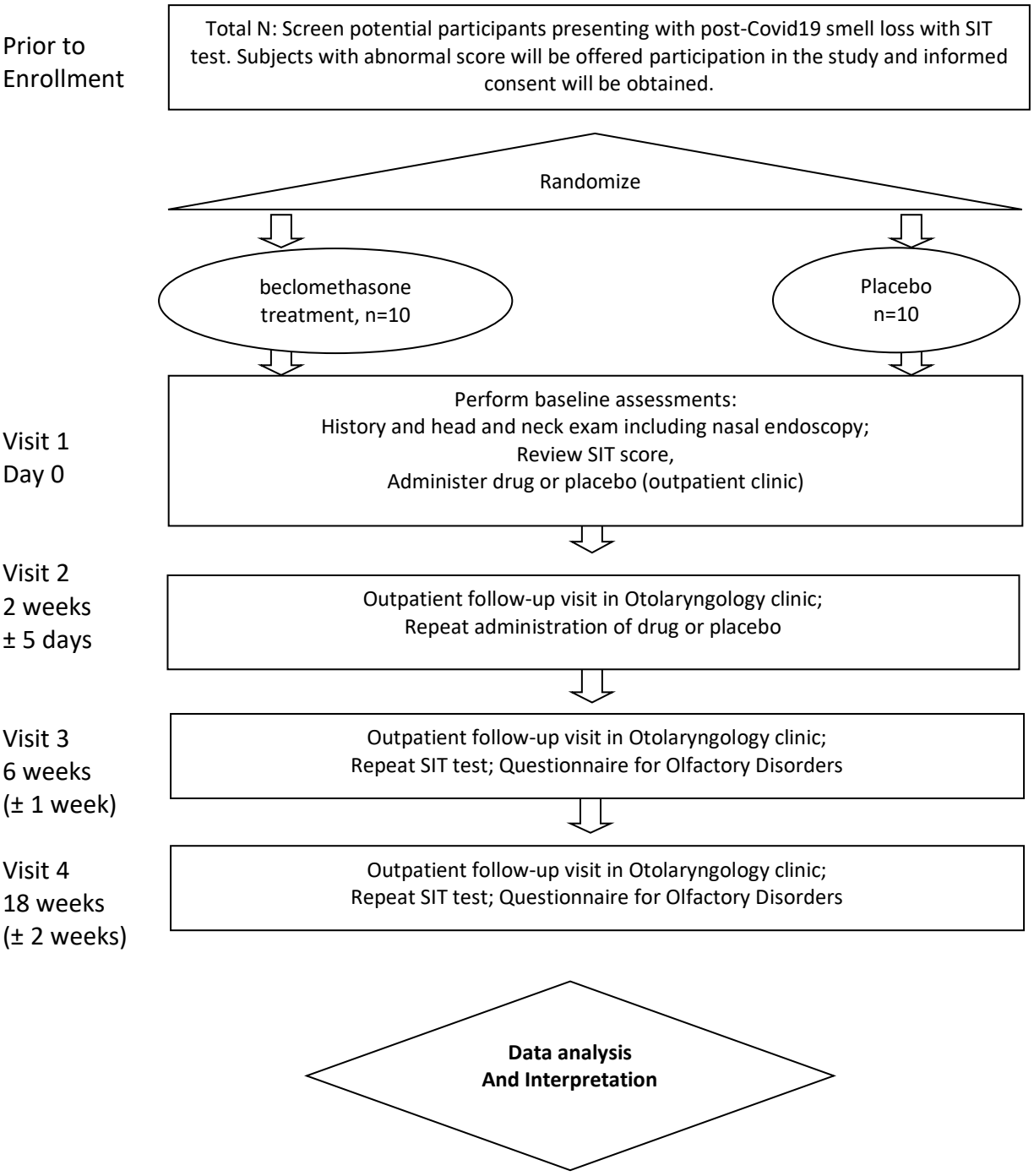
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

1.1 SYNOPSIS

Study Title:	DIRECTED TOPICAL DRUG DELIVERY FOR TREATMENT FOR PASC HYPOSMIA
Study Product:	Beclomethasone; Vectra F-microsponge ; PosiSep microsponge
Study Description:	This study will compare topical intranasal directed administration of a Vectra F or PosiSepmicrosponge with Beclomethasone versus placebo for the treatment of persistent olfactory loss due to COVID-19. We hypothesize that treatment with drug will result in improved olfactory function.
Objectives:	Primary Objective: To determine if directed topical drug treatment results in improved olfactory function, compared to placebo.
Endpoints:	Primary Endpoint: Olfactory function at 6 and 18 weeks post-enrollment. Secondary Endpoints: Olfactory-specific quality of life questionnaire.
Study Population:	Adult patients of either gender presenting to Duke Rhinology Clinic with hyposmia following COVID19 lasting > 3 months, documented by abnormal score on objective olfactory testing.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Duke University School of Medicine Head and Neck Surgery clinic.
Description of Study Intervention:	Subjects will be randomized to receive either Beclomethasone or placebo. Drug will be administered topically on an intranasal microsponge, placed in the olfactory cleft using a nasal endoscope, on Day 1 and repeated on day 14.
Study Duration:	12 months
Participant Duration:	4.5 Months

1.2 SCHEMA


Prior to Enrollment
Total N: Screen potential participants presenting with post-Covid19 smell loss with SIT test. Subjects with abnormal score will be offered participation in the study and informed consent will be obtained.
Randomize
beclomethasone treatment, n=10
Placebo n=10
Visit 1 Day 0
Perform baseline assessments:
History and head and neck exam including nasal endoscopy;
Review SIT score,
Administer drug or placebo (outpatient clinic)
Visit 2 2 weeks ± 5 days
Outpatient follow-up visit in Otolaryngology clinic;
Repeat administration of drug or placebo
Visit 3 6 weeks (± 1 week)
Outpatient follow-up visit in Otolaryngology clinic;
Repeat SIT test; Questionnaire for Olfactory Disorders
Visit 4 18 weeks (± 2 weeks)
Outpatient follow-up visit in Otolaryngology clinic;
Repeat SIT test; Questionnaire for Olfactory Disorders
Data analysis
And Interpretation

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -2 to 0	Enrollment/Baseline Day 0	Study Visit 2 Day 14 +/-5 days	Study Visit 3 week 6 +/- 1 weeks	Study Visit 4 week 18+/- 2 weeks
Informed consent	X				
Demographics	X				
Medical history	X				
Physical Exam	X				
Vital Signs[1]	X		X	X	X
Concomitant Medications Review	X				
SIT (olfaction test)	X			X	X
QOD (questionnaire)	X			X	X
Randomization	X				
Physical exam, with nasal endoscopy	X				
Administer study intervention		X	X		
Adverse event review and evaluation		X	X	X	X

1.4 TIME AND EVENTS KEY

1 – Vital Sign measurements that will be collected are heart rate, blood pressure, temperature, height and weight at a minimum. (**Note**: that height will only be collected at Screening.)

INTRODUCTION

1.5 STUDY RATIONALE

COVID19 is a common cause of olfactory loss. Studies indicate that objective smell loss lasting > 3 month occurs in up to 10% of subjects with Covid smell loss. There are no effective drug treatments available, although olfactory training therapy has been used for some forms of post-viral smell loss with limited benefits. Our recent research has identified evidence for ongoing local inflammatory changes in the olfactory area of the nose in long-COVID smell loss patients. Nasal spray meds, such as steroids, are known to not reach this region of the nose well. Therefore, we propose to test this simple pharmacologic intervention in long-COVID smell loss patients with objective olfactory loss, to directly deliver a topical nasal steroid to the olfactory cleft of the nose in an absorbable sponge. Both the medication and sponge are approved for use in the nose and sinuses.

1.6 BACKGROUND

Persistent anosmia (a loss of one's sense of smell) affects an estimated 14 million people in the US[1]. Many persistent acquired forms of anosmia are thought to be due to neurodegenerative processes such as aging (presbyosmia) or damage to the nasal olfactory neuroepithelium (post-viral or post head trauma anosmia)[2]. Of these conditions, post-COVID smell loss has emerged as a major problem, impacting >30 million people globally. **Currently, we have no treatments for this problem**.

The pathogenesis of post-COVID smell loss is incompletely understood. Our recent research suggests that post-COVID hyposmics harbor ongoing local inflammation in the mucosa of the olfactory cleft of the nose, accompanied by fewer intact olfactory neurons. Normally, damaged olfactory neurons are replaced by basal progenitor cells, but it is thought that inflammation impairs this recovery process. **We hypothesize that an intervention to deliver anti-inflammatory medication directly to the olfactory area of the nose would help promote olfactory recovery.**

In considering possible therapeutic approaches, direct endoscopic application of an absorbable sponge impregnated with a steroid medicine is attractive. Steroids such as beclomethasone are FDA approved for both topical nasal administration and have a long track record of safe clinical use. Also, a dissolvable drug delivery microsponge (Vectra and PosiSep) is approved for nasal or sinus application. The use of a microsponge is ideal, since the olfactory area of the nose sits superiorly and a simple liquid would drip to the nasal floor if applied directly, and a self-administered spray does not efficiently reach this region of the nose. Given the safety record of the microsponge and steroid, we propose to undertake a human study testing this therapy for treatment of post-COVID persistent hyposmia. Identification of an effective therapy for certain forms of anosmia would be a significant advance, as there currently are no treatments available.

1.7 RISK/BENEFIT ASSESSMENT

1.7.1 KNOWN POTENTIAL RISKS

Risks from medication: beclomethasone is FDA approved, with many-year safety history. It is widely used for topical nasal delivery for allergy or rhinitis. Potential risks of long-term use include elevated ocular pressure in subjects with glaucoma, or possibly localized nasal irritation. The Vectra microsponge and PosiSep microsponge is approved for nasal and sinus application. It is widely used to place into a narrow sinus drainage region after surgery to soak with steroid for local delivery, in an effort to prevent swelling or blockage. The material dissolves generally within 6-7 days. Potential risks include tissue injury during endoscopic placement, although this is unlikely when applying it to the olfactory cleft region between the middle turbinate and nasal septum.

Other risks: There is no economic risk, as we will supply the study medication. The pre-study work up and care is the standard-of-care, unchanged, and is no different for patients choosing or not choosing to participate in this study (nasal exam and psychophysical olfactory assessment using the Smell Identification Test (Sensonics). Psychologically, there is the risk of disappointment from possible lack of improvement or from treatment with placebo. However, the current standard-of-care is no treatment, so we will council patients regarding this.

1.7.2 KNOWN POTENTIAL BENEFITS

The immediate and long-range potential benefit is improvement in olfactory function. As stated, the standard of care for persistent post-COVID hyposmia is observation, and many patients do not recover olfaction. Translational research findings support the conclusion that effective treatment of olfactory cleft inflammation may help recovery. Thus, there is potential that olfactory neuron will improve with treatment in this study.

1.7.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Existing evidence is consistent with a very positive risk to benefit assessment. Prior clinical use of nasal steroids and the microsponge report no adverse effects. The treatment involves only 2 applications of medication. There are no existing alternatives. Basic science studies provide evidence for promoting recovery using this drug or approach.

OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine if topical intranasal treatment with beclomethasone on a microsponge results in improved olfactory function, compared to placebo.	Olfactory function at 6 weeks and 18 weekspost-enrollment, as measured by Smell Identification Test (SIT).	SIT is a validated test for olfaction. Time points were chosen to test for early recovery of olfactory neurons versus evidence for successful regeneration, respectively.
Secondary		
To assess olfactory-specific quality of life measure in treated versus placebo groups.	Questionnaire on olfactory dysfunction (QOD) scores at 6 weeks and 18 weeks .	QOD is a validated tool for measuring quality of life related to olfactory loss.
Tertiary/Exploratory		
N/A		

STUDY DESIGN

1.8 OVERALL DESIGN

- **Hypothesis**: Treatment with topical intranasal beclomethasone on a microsponge applied to the olfactory region of the nasal cavity will result in improved olfactory function, compared to placebo.
- **Phase 2 trial.**

- **Design:** Randomized, placebo-controlled, double-blind study.
- **Study groups:** Treatment versus Placebo.
- **Number of Sites:** Single site.
- **Study Intervention:** Beclomethasone on a microsponge

1.9 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We seek to determine if treatment with Beclomethasone on a microsponge will improve olfaction in post-COVID patients with persistent olfactory loss. To obtain high quality evidence, we chose a prospective randomized placebo control double blind approach. There is no standard of care treatment or drug that can be used for comparison; the current standard of care is observation. To avoid bias, a double blind approach will be used. Based on the best knowledge for mechanism of olfactory loss in these patients, we believe that directed topical nasal delivery of an anti-inflammatory to the olfactory area of the nasal cavity is likely to be effective.

1.10 JUSTIFICATION FOR DOSE

Dose regimen is based on known pharmacology of beclomethasone and known time for microsponge to dissolve. Beclomethasone is a longer-acting topical nasal glucocorticoid drug, compared to other available choices. The microsponge is designed to elute medication for about a week. We chose a single re-application at 2 weeks to deliver a total course of treatment that covers approximately one month.

1.11 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit shown in the SoA.

STUDY POPULATION

1.12 INCLUSION CRITERIA

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

1. Presents to Duke HNSCS clinic with post-COVID hyposmia lasting greater than 3 months following COVID19 by history, with olfaction documented by University of Pennsylvania Smell Identification Test (SIT).
2. Male or female, aged 18 years or older
3. Provision of signed and dated informed consent form
4. Stated willingness to comply with all study procedures and availability for the duration of the study

1.13 EXCLUSION CRITERIA

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

1. Pregnancy or lactation
2. Known allergic reactions to components of microsponge or to beclomethasone
3. Known diagnosis of glaucoma
4. Febrile illness within 1 week
5. Treatment with another investigational drug or other intervention within 3 months
6. Active sinonasal disease by nasal exam, i.e. rhinosinusitis, nasal polyps
7. Adults unable to consent
8. Prisoners, employees or subordinates
9. Individuals who are not yet adults (infants, children, teenagers). This population is excluded because the study problem is most common in adults.

1.14 LIFESTYLE CONSIDERATIONS

*N*ot Applicable

1.15 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Re-screening will not be performed.

1.16 STRATEGIES FOR RECRUITMENT AND RETENTION

- Target study sample size: 10 subjects in each arm, 20 subjects total. No exclusions by gender, race and ethnicity. Anticipated number to be screened in order to reach the target enrollment: 50 subjects.
- Anticipated accrual rate: 20 subjects
- Anticipated number of sites: 1
- Source of participants: outpatient. We routinely see smell loss subjects and expect to readily identify ample number of subjects, as no treatments are available.
- Types of recruitment strategies planned: Will list trial on clinicaltrials.gov, and will notify patient advocacy groups (Smell and Taste Association of North America, STANA; 5th Sense) that help advise smell loss patients on possible trials.

Specific strategies that will be used to recruit and retain historically under-represented populations in order to meet target sample size and conform with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects: We will not exclude any demographic (other than children, as stated); our population in Durham County is quite diverse; the study population is anticipated to reflect this diversity.

STUDY INTERVENTION

1.17 STUDY INTERVENTION(S) ADMINISTRATION

1.17.1 STUDY INTERVENTION DESCRIPTION

Subjects will be randomized to receive either beclomethasone or placebo, to be prepared by our research pharmacy. Drug will be administered intranasally by an otolaryngologist at 2 outpatient visits, using a nasal endoscope to place the delivery microsponge in the olfactory region of the nasal cavity and then applying the drug or placebo onto the microsponge. This delivery method will direct the drug to the proper region of the nasal cavity and will prevent it from rapidly leaving this location (i.e., dripping inferiorly to the nasal floor).

Beclomethasone is available by prescription as a topical nasal spray; one brand name is Beconase AQ, GlaxoSmithKline. This is a microcrystalline suspension of beclomethasone dipropionate, monohydrate equivalent to 42 mcg of beclomethasone dipropionate, calculated on the dried basis, in an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% v/w phenylethyl alcohol.

1.17.2 DOSING AND ADMINISTRATION

Drug will be administered intranasally by an otolaryngologist at 2 outpatient visits, using a nasal endoscope to place the delivery microsponge in the olfactory region of the nasal cavity and then applying the drug or placebo onto the microsponge.

1.18 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1.18.1 ACQUISITION AND ACCOUNTABILITY

Randomization, drug and placebo preparation, and packaging will be done Duke research pharmacy following their established protocols for double-blind studies. When ordered, the dose will be administered by a physician otolaryngologist in outpatient clinic.

1.18.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Research pharmacy will prepare and label study drug or placebo appropriately for double-blind study.

1.18.3 PRODUCT STORAGE AND STABILITY

Drug is to be stored at room temperature.

1.18.4 PREPARATION

No preparation will be required. Drug or placebo will be administered ontranasally by physician at 2 visits.

1.19 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To minimize bias, this will be a randomized double-blind trial. We will use the Duke Research Pharmacy to prepare study drug or placebo, using their randomization procedures and labeling. Trial randomization codes will be maintained until planned enrollment is reached and the final patient has completed the planned follow up visits. There are no planned lab studies or measures that would be expected to lead to inadvertent unblinding. If there are serious adverse events (SAEs), this will be reported to the PI and unblinding for the affected subject would be performed.

1.20 STUDY INTERVENTION COMPLIANCE

Since the drug or placebo will be applied intranasally by the physician at 2 visits, there is no need for compliance checks or verification of delivery.

1.21 CONCOMITANT THERAPY

Concomitant medications will not be restricted, except that we will ask subjects to avoid using other intrnasal spray medications such as nasal saline, nasal decongestants or allergy sprays.

1.21.1 RESCUE MEDICINE

Not Applicable

STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable).

1.22 DISCONTINUATION OF STUDY INTERVENTION

If a patient notes a possible adverse effect, such as allergic reaction to study medication, we will discontinue study medication. Any new clinically relevant finding will be reported as an adverse event (AE). Because the outpatient course of study medication is only 6 days, we will not restart study medication in that short timeframe and instead will withdraw the patient from this study. Such patients will still be offered planned follow up and the planned outcome measures will still be collected.

The data to be collected at the time of study intervention discontinuation will include the following:

- Details of possible adverse event, and appropriate care as indicated (for example ER assessment).

1.23 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced. Patients who do not complete the full course of study drug/placebo will be noted in the results tables, and they will not be included in the statistical analysis of outcome measures, since this is a simple comparison of SIT score between patients receiving 2 applications of drug versus placebo.

1.24 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the 2 scheduled follow up Otolaryngology clinic visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

SAFETY ASSESSMENTS

1.25 EFFICACY ASSESSMENTS

The primary outcome measure is olfactory ability at 6 weeks and 18 weeks, measured via the SIT. There are only 3 procedures involved in the study to assess efficacy: (1) SIT measures (2) Administration of study medication or placebo, (3) the QOD quality of life questionnaire.

- The SIT is a self-administered 40-item test involving microencapsulated (scratch-and-sniff) odors with a forced-choice design. There are 4 booklets with 10 questions each, asking the subject to identify which of 4 answers best described the odor. Total scores are categorized, based on normative data, as normal, mild hyposmia, moderate hyposmia, severe hposmia, total anosmia, or probable malingering. The test was developed at University of Pennsylvania as part of an NIH-funded program project and is widely used as a standard assessment of olfactory function.

- The QOD is a validated olfactory-specific quality of life questionnaire and is attached.

1.26 SAFETY AND OTHER ASSESSMENTS

The potential patient safety issue for the study is the possibility of adverse reaction to study medication. The dosage regimen we are using has been used as standard for this drug, as prescribed for metered dose nasal spray for rhinitis or nasal polyps. Patients will receive instructions and contact information to inform the coordinator or PI promptly of any potential problems. At follow up visit, we will collect any comments or notes regarding possible side effects.

1.27 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

1.27.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

1.27.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or at home.

1.27.3 CLASSIFICATION OF AN ADVERSE EVENT

1.27.3.1 SEVERITY OF EVENT

For adverse events (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. Of note, the term "severe" does not necessarily equate to "serious".

1.27.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

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

1.27.3.3 EXPECTEDNESS

PI will be responsible for determining whether an adverse event (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 intervention.

1.27.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (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 case report form (CRF). 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.

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.

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.

1.27.5 ADVERSE EVENT REPORTING

Adverse Event reporting will adhere to all established guidelines, as described below.

1.27.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the Duke Human Subjects Research Office any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

1.27.7 REPORTING EVENTS TO PARTICIPANTS

Any subjects who have not yet completed their first follow up visit will be contacted by phone to inform them of any Serious Adverse Events, if any occur.

1.27.8 EVENTS OF SPECIAL INTEREST

Not Applicable

1.27.9 REPORTING OF PREGNANCY

N/A

1.28 UNANTICIPATED PROBLEMS

1.28.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

1.28.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). 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 serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 5 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 1 week 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), within 1 week of the IRB's receipt of the report of the problem from the investigator.

1.28.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

STATISTICAL CONSIDERATIONS

1.29 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

To determine if treatment with topical beclomethasone applied on microsponge to the olfactory cleft results in improved olfactory function in long-COVID hyposmics, compared to placebo. Type of comparison: superiority. Time period: 6 weeks and 18 weeks post-enrollment.

Null hypothesis: There is no difference in SIT score with drug treatment or placebo.
Alternative hypothesis: Drug treatment results in improved SIT score.

- Secondary Efficacy Endpoint(s):

To assess olfactory-specific quality of life measure in treated versus placebo groups.
Type of comparison: superiority. Time period: 6 weeks and 18 weeks post-enrollment.

Null hypothesis: There is no difference in QOD score with drug treatment or placebo.
Alternative hypothesis: Drug treatment results in improved QOD score.

1.30 SAMPLE SIZE DETERMINATION

Number of participants to enroll to have adequate power to test the key hypotheses for the study:
Placebo group: 10
Treatment group: 10

- Target study sample size: 10 subjects in each arm, 20 subjects total. Anticipated number to be screened in order to reach the target enrollment: 50 subjects
- *Outcome measure used for calculations: SIT score*
- *Test statistic: t-test*
- *Null and alternative hypotheses:*
    - Null hypothesis: There is no difference in SIT score with drug treatment or placebo.
    - Alternative hypothesis: NAC treatment results in improved SIT score.

- *Type I error rate (alpha): 0.05*
- *Power level: 0.8*
- *Assumed mean and variance:*
    - Placebo group, mu1: SIT=24 ± 4
    - Treatment group, mu2: SIT=29 ± 4

Reference: "*Hypothesis Testing: Two-Sample Inference - Estimation of Sample Size and Power for Comparing Two Means"* in Rosner, Bernard Fundamentals of Biostatistics, Belmont, Calif. : Duxbury Press, [1995].

SIT score of 24 is used for the placebo group because this is a score categorized as severe hyposmia (reduced olfaction). Based on published reports and our experience with long-COVID hyposmia subjects, we anticipate identifying and enrolling patients with a mean score of approximately 24 and a variance of approximately 4.

In terms of estimated possible improvement in SIT score with drug treatment, we have chosen an increase of 5 ± 4 points, because a jump of more than a few points on a repeat SIT test after one month is considered to be greater than just random chance[3]; (and Doty, R., *personal communication*). There are no published data available for specifically measuring olfactory change following treatment with beclomethasone applied to the olfactory cleft topically for post-viral hyposia.

- *Anticipated impact of dropout rates, withdrawal, missing data, etc. on study power:* to compensate for such issues, we have increased our sample size by 1 subject per group.

- *Secondary endpoint:* We have included a secondary endpoint to measure quality of life via a validated questionnaire (QOD). We have no specific guides for mean or variance for the questionnaire in terms of possible beclamethasone or placebo treatment, so no calculations are possible. Nonetheless, a simple questionnaire poses no cost or risk, such that we see no reason to not collect these data.

1.31 POPULATIONS FOR ANALYSES

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants):

  Placebo group (n=10)
  Beclamethasone treated group (n=10)

1.32 STATISTICAL ANALYSES

General Approach

1.32.1 DATA

Data (SIT scores, QOD scores) will be presented as means with standard deviations, as well as range. Placebo and drug-treated groups will be compared statistically, with $p<0.05$ considered significant, via two-tailed t-test. If data are not normally distributed, nonparametric testing or appropriate post-hoc corrections will be applied.

1.32.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary endpoint is SIT score at 6 weeks and18 weeks.
Placebo and drug-treated groups will be compared. SIT (mean ± sd) will be compared via two-tailed t-test. SIT scores may range from 0-40, and normal scores are well-established. An assignment of normosmia, mild hyposmia, moderate hyposmia, severe hyposmia, anosmia, or probable malingering can be made based on SIT score.

1.32.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoint is QOD score at 6 weeks and18 weeks.
Placebo and drug-treated groups will be compared. QOD (mean ± sd) will be compared via two-tailed t-test.
QOD scores may range from 0-75. There are 25 quality of life questions, scored 0-3 each. A lower score implies more severe dysfunction.

1.32.4 SAFETY ANALYSES

There is no formal safety endpoint being evaluated. AEs will be counted per event and will be presented as number of AEs and severity.

1.32.5 BASELINE DESCRIPTIVE STATISTICS

The baseline characteristics of the placebo group and the drug-treated groups will be presented. Data will include age (mean ± sd) and SIT score (mean ± sd) on enrollment. Also, gender, ethnicity, and details of the Covid19 history (i.e., timing, duration, severity) will be captured.

1.32.6 PLANNED INTERIM ANALYSES

Not Applicable

1.32.7 SUB-GROUP ANALYSES

Although no differences are anticipated based on gender, we will capture this information and present mean SIT scores for males or females. The primary endpoint will include both genders.

1.32.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

A Table containing individual patient data will be included.

1.32.9 EXPLORATORY ANALYSES

Not Applicable

SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

1.33 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

1.33.1 INFORMED CONSENT PROCESS

1.33.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The consent form that will be used for this study is attached.

1.33.1.2 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. All subjects must provide written consent prior to participating in this study. Potential participants will be given an ICF containing information in a language understandable to them, which meets all federal, local, ICH and HIPAA requirements, and is approved by an Institutional Review Board (IRB).

Informed consent will be obtained using processes that comply with all federal and local regulations. Patients evaluated at Duke otolaryngology clinic for post-COVID smell loss, with documented hyposmia by University of Pennsylvania Smell Identification Test (SIT) will be identified and approached by the treating physician. The Investigator (or designee) will carefully review the ICF with potential subject, which includes a review of the purpose, scope, procedures, and potential consequences to the subject. Patients will be informed that participation in the study is completely voluntary, and they may withdraw from the study at any time with no penalty or loss of benefits. Likewise, the quality of their medical care will not be adversely affected if they decline to participate in this study.

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 family or 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 potential study subject (or healthcare proxy) and Investigator (or designee) must sign and date the ICF before the subject can participate in the study. The original will be retained on file at the study site, and the subject will receive a copy.

Should the ICF be amended during the study, the site must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects. Spanish speaking subjects will be provided a translated consent.

1.33.2 STUDY DISCONTINUATION AND CLOSURE

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 PI to study participants and the Institutional Review Board (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 that the primary endpoint has been met
- Determination of futility

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

1.33.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Each subject's name will remain strictly confidential and shall be excluded from the database, only subjects' initials, assigned identifier number, and birthdate shall be entered, uploaded, or otherwise documented in the database. The Investigator will retain a cross-referencing record of each subject's name and assigned identifier number.
All study data and results will be stored in an electronic database. Each study subject will give explicit consent for representatives of the IRB/IEC and regulatory authorities to inspect and verify each subject's medical records and collected information. Each study subject will be assured that all their personal information will be maintained in the strictest of confidence, and in compliance with HIPAA, and all other federal and local laws regulating privacy and data protection.
All research activities will be conducted in as private a setting as possible.
The study participants' contact information will be securely stored at the 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 the reviewing IRB, Institutional policies, or sponsor requirements.

1.33.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the PI's office at Duke University.
There are no specimens or biologic samples collected for this study.

1.33.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Bradley J. Goldstein, MD, PhD Associate Professor, Head and Neck Surgery & Communication Sciences	
Duke University School of Medicine	Duke University School of Medicine
40 Duke Medicine Circle, Clinic 1F, Durham, NC 27710	*40 Duke Medicine Circle, Clinic 1F, Durham, NC 27710*
919-684-6595	
Bradley.goldstein@duke.edu	

1.33.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- On-site monitoring, by the research manager of the Department will be planned throughout the study. This will included a targeted review of with verification of endpoint and safety, and the distribution of monitoring reports will be provided to the PI. Study coordinator will help following the regulations in every aspect of the study.
- Independent audits will not be conducted, for this relatively small study.

1.33.7 QUALITY ASSURANCE AND QUALITY CONTROL

An individualized quality management plan will be developed to describe a site's quality management. No specimens are to be collected for this study, and the data that are to be collected for primary endpoint include SIT scores. Thus, we will focus on monitoring that SITs, a self-administered test, are being collected and scored properly.

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 monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

1.33.8 DATA HANDLING AND RECORD KEEPING

1.33.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

This is a Single-Center study. Data collection is the responsibility of the clinical trial staff under the supervision of the PI. The PI 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. Records will be kept in the EMR at Duke, known as Epic. This will include demographics, vital signs, and initial H&P. Relevant data will be summarized on a visit worksheet, including information on initial SIT score, COVID19 history, and key exam findings.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) will be then entered into the EMR 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. Data will include the drug administration information, SIT scores and QOD scores.

1.33.8.2 STUDY RECORDS RETENTION

Study documents will be retained until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period,

however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

1.33.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH 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 GCP:

- 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 investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

1.33.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting the PI, Bradley Goldstein, MD, PhD.

1.33.11 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 design and conduct of this trial. The study leadership in conjunction with Duke University has established policies and procedures for all researchers to disclose all conflicts of interest and, will establish a mechanism for the management of all reported dualities of interest.

1.34 ADDITIONAL CONSIDERATIONS

N/A

1.35 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOD	Questionnaire on Olfactory Disorders
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIT	Smell Identification Test
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

1.36 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale