A Prospective Trial to Assess how Glycopyrronium Cloths at the Amputation Site of Limb Amputees Changes the Severity of Hyperhidrosis and the Fit and Function of the Prosthetic Measured by Patient Reported Outcomes.

BACKGROUND:

Approximately 1 in 190 people in the United States have experienced a limb amputation. Of these patients with amputations, over sixty percent suffer from hyperhidrosis at the amputation site. Amputation site hyperhidrosis interferes with these patients' daily activities as well as their ability to engage in vigorous activity beneficial to their overall health. In fact, amputees identified heat and sweating as what reduces their quality of life more than any other problem, even pain. Despite the significant impact hyperhidrosis has on amputees' quality of life and ability to stay physically active, there are no self-administered, non-invasive, well-tolerated treatments for amputation site hyperhidrosis. Botulinum toxin injections are an available treatment option for focal hyperhidrosis. However, the large surface area covered by the prosthetic and prosthetic sleeve often necessitates very large volumes of botulinum toxin for effective treatment at amputation sites. This is costly, making it difficult to be able to treat the entire affected area. Botulinum toxin also requires office visits and repeat treatments every 4-6 months.

Glycopyrronium cloths are a unique treatment possibility, because they can easily be used over a large body surface area and can easily be self-administered at home. At this time, glycopyrronium cloths are only FDA approved for use in the axillae. There are two primary differences between the use of these cloths at amputation sites and axillae: 1) the amputation site is occluded during daytime hours by the prosthetic and 2) the area treated for amputation-site hyperhidrosis (the entire area covered by the prosthetic sleeve) is typically a much larger surface area than the axillae. These factors could significantly increase systemic absorption of glycopyrronium and cause systemic side effects. In order to minimize these effects, the medication will be applied at night, when the site is not occluded. Frequent visits with the investigator will also encourage early reporting of symptoms which could be the result of systemic side effects associated with use on a larger surface area.

PURPOSE & OBJECTIVES

Primary Objectives

1. Determine if daily use of glycopyrronium cloths applied to the amputation site decreases hyperhidrosis severity and improved fit and function of the prosthetic as measured by patient reported outcome measures.
2. Determine if patient's disease-related life quality is changed as a result of glycopyrronium cloth use as measured by the SKINDEX-16.

Secondary Objectives

1. Evaluate the safety and side effects of glycopyrronium cloths used at amputation sites in patients wearing a prosthetic. This is necessary because using this product on a large area of skin, which is also occluded (covered by a prosthetic and prosthetic sleeve), may result in more systemic absorption and/or local irritation than previous studies at different and usually smaller area sites.
2. Determine if patient has change in activity level based upon the measurements of the activity monitor.

Primary Endpoints

1. Determine the change in ASDD-m Impact scores between the end of the treatment and placebo periods.

Secondary Endpoints

1. Determine the change of the weekly average of the Axillary Sweating Daily Diary (ASDD-m) (completed daily), the Hyperhidrosis Disease Severity Score (HDSS) (completed weekly) and Prosthetic Fit and Function Questionnaire (PFFQ) (completed weekly) scores between treatment and placebo periods. As patients will cross-over between placebo and treatment groups, patients serve as their own control.
2. Determine the change in SKINDEX-16 scores between treatment and placebo periods.
3. Describe the frequency and degree of local and systemic adverse events and suspected side effects using glycopyrronium cloths at amputation sites.
4. Determine the change in activity in patients by comparing the change in the average daily step count of weeks using the study treatment to weeks not using the study treatment (screening period and 4 weeks of placebo).

STATISTICAL CONSIDERATIONS

Because there is large variation between the size of the application sites between patients, which is dependent on the particular prosthetic and prosthetic sleeve (making sweat volume highly variable), and because the primary objective of the study is to improve prosthetic fit and function, we have opted to use patient-reported outcomes (PROs) as the primary endpoint.

As we are using PROs, we have chosen to structure the analysis of the PROs similarly to the two large studies in which glycopyrronium cloths was evaluated for primary axillary hyperhidrosis in phase III trials (ATMOS-1 and ATMOS-2).

Assessments using proportion testing:

1. HDSS: Scores will be collected at weeks 0, 1, 2, 3, 4, 5, 6, 7, 8, 9. a 2-point improvement has been associated with an 80% reduction in sweating. Those with a >= 2 point improvement will be considered responders.
2. ASDD-m: Scores will be collected at baseline and then weekly scores will be the average of the daily scores for each question. The patient must report 4 days/week for the weekly score to be calculated. Each question will be analyzed separately. Item 2 on the ASDD measures sweating severity. Those with a >= 4 point improvement over baseline are considered responders.

Assessment of score changes will be assessed using proportion testing;

3. PFFQ, SKINDEX-16 and ASDD-m Impact

Sample size calculation:

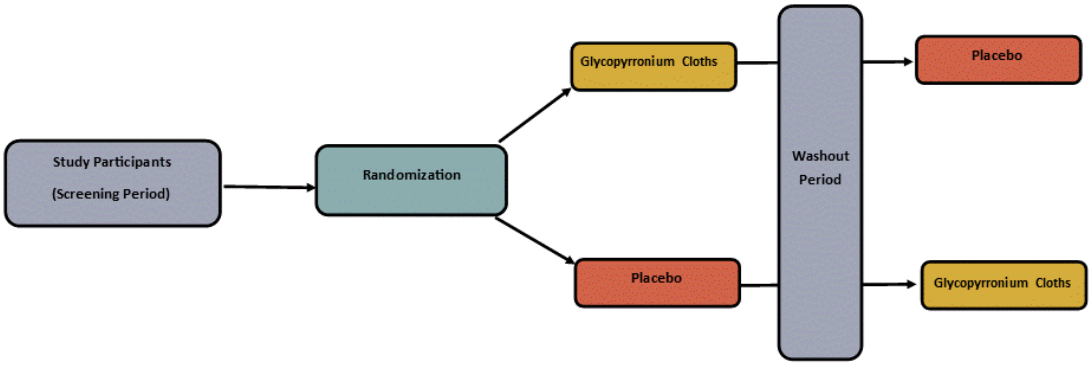
Using the ASDD endpoint and based on data from the ATMOS-1 and ATMOS-2 trials, the provided parameters were: significance level (adjusted for sidedness) = 0.025 (0.05 two-sided), standard deviation of the difference = 1.7, power = 0.8, difference in means = 4.

The variable calculated was the total number of patients.

A total of 4 patients will be needed to enter this two-treatment crossover study. The probability is 86 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 4 units. This is based on the assumption that the standard deviation of the difference in the response variables is 1.7. Assuming a standard deviation of 3.0, the necessary sample size will increase to 7. Allowing for patient dropout of 10% (comparable to the ATMOS studies), a total of at least 8 patients should be enrolled to allow for adequate statistical power.

STUDY DESIGN:
This is a Prospective, Double Blinded, Placebo Controlled, Randomized, Cross-over trial.
Participants will be randomized, using a 1:1 ratio, to one of 2 arms:

- **Arm #1:** At Baseline participants will receive active treatment for 4 weeks, completing a 1 week wash out period and then concluding with 4 weeks of placebo treatment
- **Arm #2:** At baseline participants will receive placebo for 4 weeks, completing a 1 week washout period and then concluding with active treatment for 4 weeks.



PARTICIPANT ELIGIBILITY
Inclusion criteria:

1. History of limb amputation with limb-amputation surgery at least 6 months ago
2. Have a prosthetic device
4. HDSS of 3 or greater (at screening)
5. ASDD-m Item 2 severity score >= 3 (at screening)
6. PFFQ score >= 4 (at screening)

Exclusion criteria:

1. Open sores or wounds on residual limb (at screening and baseline)
2. Known sensitivity to glycopyrronium tosylate or other component of Qbrexza
3. Pregnant or lactating.
4. Use of botulinum toxin within 6 months of the baseline visit
5. Use of topical aluminum chloride within 1 month of the baseline visit
6. Any significant concurrent condition that could adversely affect the patient's participation and/or the assessment of the safety and efficacy in the study in the opinion of the investigator

Recruitment:

Participants will be recruited or identified for inclusion in the study using in-person contact, referrals, and written or electronic record review. Patients who appear to be eligible for the study will be approached during regular clinic visits by study personnel. Providers in and outside of our institution regularly send patients to be considered for studies and these patients will be pre-screened by study personnel (coordinators and investigators) by phone and/or in person. Electronic record review may be used to find possible subjects from existing patients. One of Dr. Klein's primary site of practice is at the VA, and she will be recruiting from her clinics at the VA. We will not be cold calling any patients.

STUDY PROCEDURES:

Informed Consent – The informed consent process must be followed to ensure that potential study patients have all necessary information to make an informed decision about whether to participate in the study and that they understand their rights as a research subject during and after their participation in the study. The informed consent process follows the required elements contained in the IRB-approved informed consent form (ICF). The investigator and/or study team will explain the study accurately, in simple-to-understand language, and to encourage the patient to ask questions. This consent must be dated and retained by the Principal Investigator as part of the study records. A copy shall be given to the person signing the form. The informed consent process will be recorded in the source documentation. The informed consent process will be completed prior to conducting any study procedures.

Inclusion/Exclusion Criteria - Eligibility Criteria will be reviewed at visits 1 and 2.

Randomization - Participants will be randomized to one of 2 arms: beginning with either treatment or placebo x 4 weeks (per randomization), completing a 1 week wash out period and then concluding with treatment (if previously in the placebo group) or placebo (if previously in the treatment group) x 4 weeks.

Study Medication - Participants will be asked to apply glycopyrronium cloths or placebo cloths (based on randomization) nightly to the portion of the amputation site occluded by the prosthetic during each of the 4 week treatment periods. A treatment area will be identified based on the fit of the prosthetic at the first visit and the participant will be asked to apply the cloth to this area during the study. Treatment area will be identified, marked and photographed to aid participant in applying medication to the same and entire area.

Study Visits - Participants will complete 4 study visits with investigator (weeks 0, 4, 5, 9).

Daily PRO - Participants will be asked to complete 1 short questionnaire daily during the 2 active periods of the study (not during the washout period): the ASDD-m.

Weekly PRO - The PFFQ, HDSS, SKINDEX-16 and ASDD-m IMPACT will all be completed weekly over the course of the study. These will be collected online and monitored by study coordinator to ensure regular completion.

Local Skin Reaction Monitoring - At each visit, participants will be asked about local skin reactions

Vital signs – Vital signs including blood pressure, heart rate and temperature will be collected at each in person study visit. Vital signs may not be collected at virtual visits.

Adverse Event Monitoring – Participants will be asked about adverse events in a non-specific manner using open-ended questions. An AE is any untoward medical occurrence, including any unfavorable and unintended sign, symptom, or disease (new or exacerbated) in a patient that is temporally associated with the use of study intervention, whether or not considered related to the test article.

Activity Monitoring - An activity monitor will be used to measure daily step counts. If patients remain eligible for the study at the end of the first visit, they will be provided with an activity monitor. Participants will be instructed to wear the devices during the day and night. Participants will need to charge the device when the battery is low. Patients will report the number of daily steps to the study

coordinator weekly. Changes in daily step counts will be used for a key secondary endpoint analysis. At the end of the study, participants will be allowed to keep the devices.

Patient Reported Outcomes -

1. **Hyperhidrosis Disease Severity Scale (HDSS)** - completed weekly - The HDSS is a validated measure of hyperhidrosis severity, for which the patient assigns a single number on a four-point point scale to evaluate the impact of their current hyperhidrosis. A 2 point or greater decrease of score indicates improvement and has been associated with an 80% reduction in sweat production. While helpful, the questions on the HDSS aren't able to separate two important components: tolerability and interference with daily activities, necessitating additional questionnaires. We have revised this questionnaire to ask about sweating at the amputation site, instead of underarm sweating.
2. **Axillary Sweating Daily Diary-modified (ASDD-m) -** completed daily - The ASDD is a recently developed patient-reported outcomes tool which asks patients to complete a daily 4 item assessment tool to measure the presence, impact, severity and bothersomeness of their hyperhidrosis. While this tool was designed for axillary sweating, it is easily modified to assess amputation site hyperhidrosis. ASDD-m item 2 is a measurement of sweat severity and responders are defined as those with a >= 4 point improvement from baseline We have revised this questionnaire to ask about sweating at the amputation site, instead of underarm sweating.
3. **Prosthetic Fit and Function Questionnaire (PFFQ) - completed weekly -** A two-question questionnaire using a 5-point Likert scale to assess the fit and function of the patient's prosthetic. This questionnaire is not validated but will be utilized because it includes unique questions regarding prosthetic fit and function. We have revised this questionnaire to ask about sweating at the amputation site, instead of underarm sweating.
4. **SKINDEX-16- completed weekly.** A 16 question validated questionnaire specifically targeting the impact of skin disease on patients.

SCHEDULE OF ACTIVITIES

	Screening (-14 days)	Baseline/ Week 0	Visit 3/ Week 4	Visit 4/ Week 5	Visit 5/ Week 9
Informed Consent	X				
Inclusion/Exclusion Eligibility Review	X	X			
Treatment Area identified, marked, and photographed		X			
Adverse Event/local skin reaction Monitoring	X	X	X	X	X
Vital Signs	X	X	X	X	X
Daily Questionnaire – ASDD-m	X---------	----------	----------	----------	----------
Weekly Questionnaire – PFFQ, HDSS, Skindex-16, and ASDD-m IMPACT	X---------	----------	----------	----------	----------
Activity Monitoring	X---------	----------	----------	----------	----------
Pregnancy Testing (for females of child bearing potential)	X	X	X	X	X
Randomization		X			
Dispense Study Treatment		X	X	X	X

REMOTE VISITS:

All visits, except screening, may be conducted remotely. Remote visits may be conducted as MyChart Virtual Visits, or over the telephone. If visits are conducted remotely all study activities except vital signs will still be conducted. If it is known that a patient is going to do visits remotely, then the 'Treatment Area identified, marked, and photographed' will be done in person at the screening visit (instead of the baseline visit). At screening the coordinator will ensure that the patient has MyChart access for virtual visits and for sending questionnaires. Patient questionnaires will be sent to the patient via MyChart (or emailed if the patient prefers) for the patient to complete. Patient will return questionnaires via MyChart (or email if the patient prefers) to a member of the study team. Female participants of child bearing potential will be given home pregnancy tests at the screening visit. Participants will be required to take the pregnancy test and send a picture of the result to the study team. Pregnancy test must be negative before the study site sends the study drug to the participant. Study drug will be mailed to participants after each dispensing visit. A pre-paid return envelope will also be sent to participants to return the unused drug and used drug containers for IP accountability.

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