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Open-Label Cohort Study to Evaluate Efficacy and Safety of Application of Glycopyrronium Cloth, 2.4% for Palmar Hyperhidrosis

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ABSTRACT

Background: Hyperhidrosis of the palms has a significant negative impact on quality of life. There is no FDA-approved treatment; however, clinicians often use glycopyrronium cloth off-label for this indication despite the lack of published guidance on optimal method of application for treatment of palms.

Objective: To compare the safety and efficacy of 4 different methods of application of glycopyrronium cloth to give clinicians guidance when treating palmar hyperhidrosis.

Study Design: This study, conducted completely virtually using live interactive telemedicine, compared application times of 15 minutes, 30 minutes, and overnight without occlusion and 30 minutes under occlusion. The primary endpoint was a decrease in the mean of the Hand Severity Score (HHS) after 4 weeks of once-daily application. Safety data, including local skin reactions and other adverse events, were tabulated by cohort.

Results: Of the application times and methods tested, 30 minutes without occlusion produced the greatest decrease in the HHS with an acceptable safety profile. The most common adverse event was unilateral mydriasis, which presumably occurred from inadvertent introduction of study drug into the eye despite multiple warnings to the subjects to avoid eye contact. A few subjects had adverse events presumably due to systemic absorption of the drug similar to those seen in the pivotal trials for treatment of axillary hyperhidrosis.

Conclusion: Glycopyrronium cloth can be used successfully to treat palmar hyperhidrosis. Occlusion for 30 minutes had the poorest response presumably due to the increased sweating causing dilution of the study drug.

ClinicalTrials.gov: NCT04906655

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INTRODUCTION

Hyperhidrosis (HH) is a disorder of eccrine sweat production in an amount in excess of what is needed for thermoregulation. It is estimated that HH affects 4.8% of the US population or about 15.3 million people and produces a significant impact on quality of life.[1-4]

Glycopyrronium tosylate cloth (GC) (QBREXZA® Journey Medical Corporation, Scottsdale, Arizona) is a topical anticholinergic approved in the U.S. in 2018 for treatment of primary axillary hyperhidrosis in patients ≥9 years.[5-7] In an algorithm for treatment of primary axillary hyperhidrosis developed by the International Hyperhidrosis Society, GC and topical antiperspirants are recommended as first-line treatment.[8] Clinicians often use GC off-label to treat body areas other than the axilla, especially the palms, but there is no published guidance on efficacy, safety, or optimal method of palmar applications. Oral anticholinergics are commonly used off-label to treat hyperhidrosis of the palms and other body areas, but their utility is often limited by anticholinergic adverse effects, such as dry mouth and blurred vision, which can occur at doses required for efficacy.[9]

The purpose of this study was to compare four different methods of palmar application of GC using Patient-Reported Outcomes (PRO's) to determine if a difference in efficacy and/or safety could be determined with different methods of application. There was no placebo-control group, and there were no statistical analyses performed, so determination of the true efficacy for treatment of palmar HH with GC was not the purpose of and cannot be determined by this study.

Study Design and Subject Selection

One hundred twenty subjects, age nine years or older, with self-reported excessive sweating of the palms, who met the

inclusion criteria for severity were enrolled into a single-site, investigator-initiated, open-label cohort study of four different application methods of 2.4% GC with the objective of determining an optimal application method for treatment of palmar hyperhidrosis. All visits for this study were conducted entirely virtually using HIPAA compliant video technology.

During screening, subjects completed a daily online diary responding to the severity, impact, and bother of their palmar sweating over the preceding 24 hours. The Hand Sweat Severity (HSS) (primary endpoint) was collected electronically nightly. The Hyperhidrosis Disease Severity Scale (HDSS), the Patient Impression of Severity (PIS), and the Patient Impression of Change (PIC) were collected at the scheduled telemedicine visits. The duration of the study for each subject was approximately five weeks: 7-28 days for screening and 4 weeks of study treatment. The study was registered on ClinicalTrials.gov on September 21, 2020, identifier: NCT04906655. Institutional Review Board (IRB) approval for the original protocol was obtained from Advarra IRB on August 20, 2020, and the protocol amendment was approved by the same IRB on February 17, 2021. Screening started on October 1, 2020, and enrollment was completed on April 15, 2021. The last patient completed the study on May 20, 2021. To comply with rules for telemedicine all subjects were residents of the state of Virginia.

Key inclusion criteria for entry were self-reported excessive sweating of the palms for at least 6 months and an average HSS of ≥4 (on a scale of 0-10) during the screening period. Key exclusion criteria included pregnancy or lactation, secondary hyperhidrosis, prior sympathectomy, open wounds or infection on the hands, concomitant use of iontophoresis, botulinum toxin, experimental therapy, or unstable doses of systemic anticholinergic medications. Subjects were allowed to enroll into only one cohort. Investigational product (IP) was shipped overnight to subjects that were eligible for participation.

The treatment cohorts, application methods, and subject instructions are displayed in Table 1. For all treatment cohorts, the subjects were instructed to wipe the hands continuously until the cloth was dry (approximately 3 minutes), following the instructions in Table 1. The importance of vigorous hand washing following the application time was repeated several times to all subjects so that they understood the importance of avoiding contact of the product with the eyes.

Patient Reported Outcomes (PRO's)

The Hand Sweat Severity (HSS) was used as a PRO and was collected nightly. This PRO is a modification of the validated Axillary Sweating Daily Diary (ASDD) Item 2 for adults and children[10] which asks the subject to rate hand sweating during the past 24 hours on a 0 to 10 scale of "No sweating at all" to "Worst possible sweating". The mean change of the HSS from the week of Screen-Baseline (Day -7 to Day 0) to the final week of study treatment was the primary endpoint of this study. Subjects must have completed the HSS for at least four days within the seven days prior to Day 0 (End of Screening Visit) to qualify.

Subjects also completed two impact and bother PRO questions nightly, which asked the subject to assess the impact of their palmar sweating on their activities and how bothered they are by their palmar sweating, each on a 0 to 4-point scale.

At 4 time points in the study, subjects were also asked to rate their impression of severity and an impression of change of sweating, each on a 0 to 4-point scale. They also completed the Hyperhidrosis Disease Severity Scale.

Adverse Events (AE)

All adverse events were reported, and the Investigator determined causality and degree of severity for each.

Local Skin Reactions (LSRs)

All subjects were virtually assessed for LSRs by live interactive telemedicine. Subject LSRs included burning/stinging and pruritus and were reported by the subject verbally. Investigator LSRs included edema, erythema, dryness, and scaling. Each LSR was scored as 0 (None), 1 (Mild), 2 (Moderate), or 3 (Severe).

Adverse Events of Special Interest

Blurred Vision

Subjects who complained of blurred vision and who had no history of introduction of study drug into the eye(s), were evaluated to rule out any serious acute condition. Study drug was paused until the blurred vision resolved

Urinary Retention

For subjects who had symptoms suggestive of urinary hesitancy or retention, study drug was paused until the symptoms resolved.

Dosing Modifications

Dose interruptions of 1 to 3 days were allowed if a subject experienced treatment-related adverse events such as blurred vision, pupil dilation, significant urinary hesitation or retention, or local irritation. After resolution, once daily dosing was resumed. If a subject was unable to restart medication after a maximum of a three-day hold, the subject was withdrawn from the study. All AE's requiring dose interruption were followed until resolved.

RESULTS

Demographics and hyperhidrosis history were generally similar for all 4 cohorts (Table 2).

TABLE 1.

Application Methods and Subject Instruction for the Four Cohorts

Cohort	Application Method	Specific Subject Instructions
A	30 minutes residence time in cotton gloves	1. Complete daily diary. 2. Remove all jewelry. 3. Tear open the top of the pouch at the notch. 4. Wash hands thoroughly with warm water, and dry them. 5. Remove the wipe from the pouch and unfold the wipe. 6. Wipe both hands with the wipe continuously until the wipe is dry (up to 3 minutes). 7. Return the wipe to the pouch and put it back in the box. 8. Carefully put cotton gloves on both hands. 9. Set timer for 30 minutes. 10. After 30 minutes, remove gloves and throw them away. Immediately wash hands ***thoroughly*** with warm water and soap, and dry them.
B	30 minutes residence time under occlusion	1. Complete daily diary. 2. Remove all jewelry. 3. Tear open the top of the pouch at the notch. 4. Wash hands thoroughly with warm water, and dry them. 5. Remove the wipe from the pouch and unfold the wipe. 6. Wipe both hands with the wipe continuously until the wipe is dry (up to 3 minutes). 7. Return the wipe to the pouch and put it back in the box. 8. Carefully put occlusive gloves on both hands. 9. Set timer for 30 minutes. 10. After 30 minutes, remove gloves and throw them away. Immediately wash hands ***thoroughly*** with warm water and soap, and dry them.
C	Overnight in cotton gloves	1. Complete daily diary 2. Remove all jewelry. 3. Tear open the top of the pouch at the notch. 4. Wash hands thoroughly with warm water, and dry them. 5. Remove the wipe from the pouch and unfold the wipe. 6. Wipe both hands with the wipe continuously until the wipe is dry (up to 3 minutes). 7. Return the wipe to the pouch and put it back in the box. 8. Carefully put on the cotton gloves on both hands and go to bed. 9. In the morning, after ***at least*** 4 hours of wearing the gloves, remove the cotton gloves and throw them away. 10. Immediately wash hands ***thoroughly*** with warm water and soap, and dry them.
D	15 minutes residence time in cotton gloves	1. Complete daily diary. 2. Remove all jewelry. 3. Tear open the top of the pouch at the notch. 4. Wash hands thoroughly with warm water, and dry them. 5. Remove the wipe from the pouch and unfold the wipe. 6. Wipe both hands with the wipe continuously until the wipe is dry (up to 3 minutes). 7. Return the wipe to the pouch and put it back in the box. 8. Carefully put cotton gloves on both hands. 9. Set timer for 15 minutes. 10. After 15 minutes, remove gloves and throw them away. Immediately wash hands ***thoroughly*** with warm water and soap, and dry them.

Primary Endpoint

In the 4 cohorts, the overall mean change in the HSS from screening to end of study (week 4) was 4.2 in Cohort A, 2.6 in Cohort B, 4.0 in Cohort C, and 2.6 in Cohort D (Figure 1).

Secondary Endpoints

The mean changes in HDSS from end of screening to end of study were 0.9 in Cohort A, 0.7 in Cohort B, 1.2 in Cohort C, and 0.9 in Cohort D (Figure 2).

The mean difference of Patient Impression of Severity (PIS) from end of screening to end of study (week 4) was 1.6 in Cohort A, 1.1 in Cohort B, 1.8 in Cohort C, and 1.4 in Cohort D (Figure 3).

Adverse Events (AE's)

A total of 112 AE's were reported in the study. Of the 119 subjects that that used at least one dose of investigational product, 51 had at least one AE. There were 45 AE's unrelated to study drug across all cohorts (9 in Cohort A that affected 6 subjects, 15 in

FIGURE 1. Mean change in Hand Sweat Severity Score.

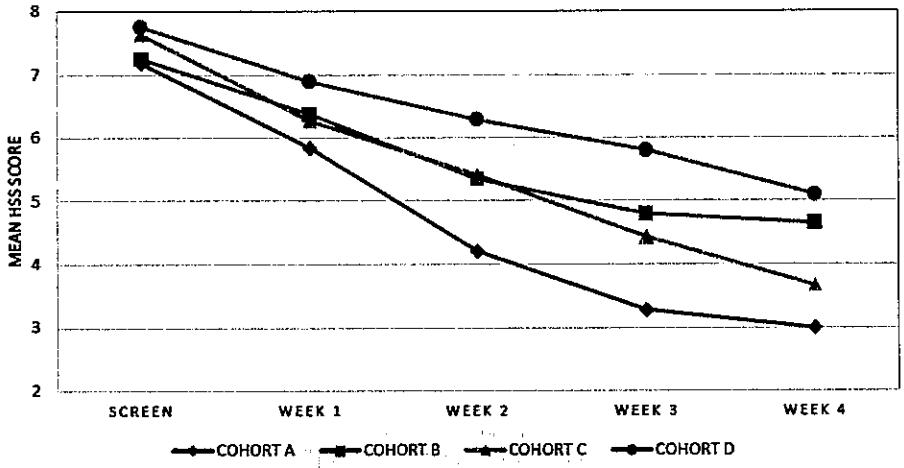

FIGURE 2. Mean change in HDSS (Hyperhidrosis Disease Severity Scale).

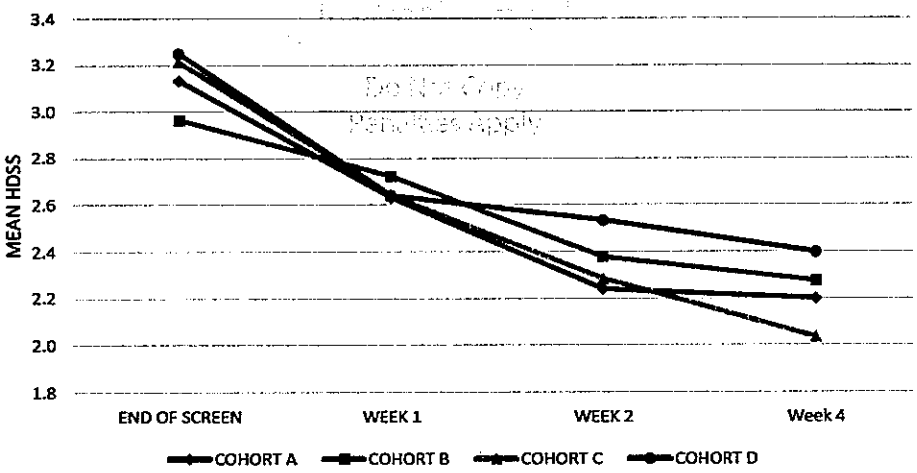

FIGURE 3. Mean change in Patient Impression of Severity.

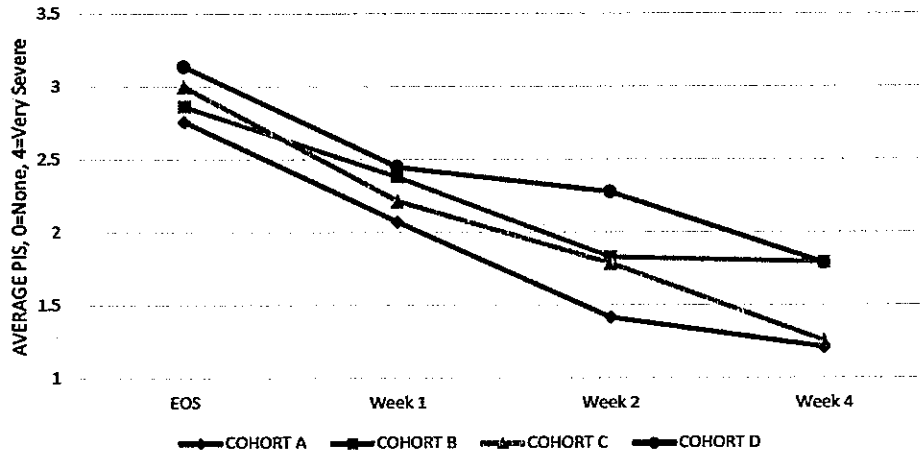

TABLE 2.

Demographics and Hyperhidrosis History					
Demographics	**Cohort A**	**Cohort B**	**Cohort C**	**Cohort D**	**Total**
Age					
Average Age:	31	28	28	27	29
Age Range	15-50	13-56	9-55	13-55	9-56
# of Adults	28	25	24	22	99
# of Juveniles	2	5	6	8	21
Age 9-15	1	3	5	3	12
Age 16-17	1	2	1	5	9
Ethnicity					
Hispanic	3	4	2	2	11
Non-Hispanic	27	26	28	28	109
Race					
Asian	3	1	2	3	9
Black or African American	5	4	4	6	19
Multi-racial	1	1	3	5	10
Native American or Alaska Native	0	0	0	1	1
Pacific Islander or Native Hawaiian	0	1	0	0	1
White	21	23	21	15	80
Sex					
Female	16	20	18	19	73
Male	14	10	12	11	47
Hyperhidrosis History					
Mean duration (years)	20.6	20.9	18.2	17.6	19.5
Duration Range	4-46	4-57	2-41	4-47	2-57
% with ONLY Palmar HH	13.3	6.7	13.3	10.0	10.8
% with HH Family History	60.0	50.0	43.3	66.7	55.0

Cohort B that affected 9 subjects, 11 in Cohort C that affected 8 subjects, and 10 in Cohort D that affected 9 subjects). There were 67 AEs related to study drug across all cohorts (15 in Cohort A that affected 5 subjects, 14 in Cohort B that affected 9 subjects, 31 in Cohort C that affected 15 subjects, and 7 in Cohort D that affected 7 subjects;Table 3).

There were 8 reported Adverse Events of Special Interest (AESI) across all cohorts that involved 7 subjects, 7 reported events of blurred vision, and 1 of urinary hesitancy. Three subjects terminated from the study early due to AEs related to treatment. One subject from Cohort A had AESIs of blurred vision and urinary hesitancy as well as AEs of bilateral pupil dilation, dry mouth, and headache and chose to withdraw. One subject from Cohort C prematurely discontinued the study because of inability to tolerate burning and itching in the treatment area, which was judged to be related to the study drug. One subject was required per protocol to withdraw because of prolonged unilateral pupil dilation that did not resolve after a 3-day hold on IP. All subjects that discontinued the study due to treatment-related related AEs were followed to resolution.

Subject reported local skin reactions were generally mild and resolved despite continuation of treatment (Table 4) while Investigator-reported local skin reactions were mild to moderate (Table 5).

There was one Serious Adverse Event (SAE) that affected a subject in Cohort C, which was unrelated to the study drug. The subject was involved in an automobile accident and suffered injuries that necessitated two surgeries, which required overnight hospital stays. The subject did not withdraw due to the SAE, though he missed some doses, not enough to be dropped from the study.

TABLE 3.

Adverse Events Related to Study Drug					
Adverse Event	**Cohort A**	**Cohort B**	**Cohort C**	**Cohort D**	**Total**
Bilateral Blurred Vision*	2	2	0	0	4
Unilateral Blurred Vision*	1	2	0	0	3
Bilateral Eye Pain	0	0	2	0	2
Photophobia	1	0	0	0	1
Bilateral Pupil Dilation	2	1	2	0	5
Unilateral Pupil Dilation	2	3	4	3	12
Urinary Hesitancy*	1	0	0	0	1
Dry Mouth	1	0	2	0	3
Dry Tongue	1	0	0	0	1
Dry Throat	0	1	0	0	1
Dry Nose	0	0	1	0	1
Headache	2	0	0	0	2
Itching in Treatment Area	1	0	3	2	6
Tingling in Treatment Area	1	2	0	0	3
Burning in Treatment Area	0	1	1	1	3
Stinging in Treatment Area	0	1	1	0	2
Xerosis & Fissuring in Treatment Area	0	1	0	0	1
Dermatitis (Dorsal Hands)	0	0	2	0	2
Dryness (Dorsal Hands)	0	0	6	0	6
Dry Cuticles	0	0	1	0	1
Excessive Dryness in Treatment Area	0	0	6	1	7
*Adverse Event of Special Interest TOTAL	15	14	31	7	67

TABLE 4.

Subject-Reported Local Skin Reactions			
Pruritis	**Week 1**	**Week 2**	**Week 4/ET**
Cohort A	1 (mild)	1 (mild)	1 (mild)
Cohort B	0	0	0
Cohort C	2 (1 mild, 1 severe)	0	1 (mild)
Cohort D	1 (mild)	1 (moderate)	0
Stinging/Burning	**Week 1**	**Week 2**	**Week 4/ET**
Cohort A	0	1 (mild)	1 (mild)
Cohort B	0	1 (mild)	1 (mild)
Cohort C	1 (mild)	0	0
Cohort D	0	0	0

TABLE 5.

Investigator-Reported Local Skin Reactions				
	Week 1	**Week 2**	**Week 3**	**Week 4/ET**
Cohort A	1 (mild erythema)	0	0	1 (moderate scaling)
Cohort B	1 (moderate dryness)	1 (mild dryness)	0	0
Cohort C	2 (1 moderate dryness & scaling 1 mild dryness & scaling)	1 (mild dryness)	0	1 (moderate dryness & scaling)
Cohort D	0	1 (mild dryness & scaling)	0	0

DISCUSSION

Glycopyrronium cloth (GC) is approved by the FDA for treatment of primary focal axillary hyperhidrosis and is considered by the International Hyperhidrosis Society as first line therapy for this indication along with antiperspirants. There is no topical or systemic medical treatment approved for treatment of palmar hyperhidrosis and clinicians often use GC off-label to treat primary focal hyperhidrosis in this and other body locations. This study evaluated four application methods to determine if there was an effect on efficacy and safety of different times of exposure to the drug and whether or not occlusion had an effect. The Prescribing Information for GC treatment of the axilla calls for the patient to wipe each axilla once and then discard the cloth. This method of dosing does not use all the medication in the cloth.

Because of the relative thickness of the stratum corneum of the palm versus the axilla and the assumption that it would take more drug to have an effect on the palms than on the axilla, we elected for this study to apply all the medication in the cloth by instructing the subjects to wipe the hands until the cloth was dry, which takes about 3 minutes. It was assumed, but not measured, that a larger dose would be delivered by this method and might produce a better effect on efficacy than a single wipe. The safety of such a potential larger dose and the expected added exposure from occlusion was unknown and was the primary reason why the study was constructed in cohorts so that the efficacy and safety of shorter contact and occlusion times could be evaluated before advancing to longer contact and occlusion times.

The four application methods in the original protocol called for 30 minutes under cotton gloves, 30 minutes with occlusion, overnight under cotton gloves, and overnight under occlusion. When it became clear that 30 minutes under occlusion was producing inferior efficacy versus non-occlusion, the fourth cohort was modified by an IRB approved protocol amendment to omit the occlusion and apply the GC under cotton gloves for 15 minutes. It is postulated that the occlusion may have stimulated even more sweating which could have "washed out" the effect of the drug.

In the pivotal studies for treatment of axillary hyperhidrosis with GC approximately 50% of the response obtained at the week 4 endpoint was observed by week 1. In contrast, much less than 50% of the total response obtained at week 4 in this study was observed by week 1. This observation may support the concept of a slower response rate for palms and the need for a longer treatment duration in any future palmar study.

CONCLUSION

In this uncontrolled open label study of four methods of application of GC, 30 minutes under cotton gloves produced the best efficacy by the several parameters studied. Although overnight under cotton gloves produced nearly the same efficacy, there were over twice as many adverse events related to treatment compared to 30 minutes. Fifteen minutes under cotton gloves produced less efficacy than 30 minutes or overnight and had substantially fewer adverse events. Thirty minutes under occlusion had about the same adverse event profile as 30 minutes under cotton gloves but the efficacy was substantially less, possibly due to the increased sweating caused by the occlusion, which may have diluted the therapeutic effect. When the efficacy result in subjects who had only palmar sweating was compared to those who had sweating in the palms and other areas, there was a greater improvement in the HSS in those subjects with palmar only sweating in all cohorts. The number of subjects with only palmar sweating represented about 10% of the total population, so the numbers are small and may not be meaningful.

Randomized vehicle-controlled studies are needed to properly characterize the efficacy and safety of glycopyrronium cloth for the treatment of palmar hyperhidrosis. Because all cohorts were showing continued improvement at week four, perhaps a longer treatment period would have yielded better results. The current study should help inform development of such a protocol.

DISCLOSURES

D.P.: Investigator and/or consultant for Dermira/Lilly, Brickell Biotech; E.R. and D.B.: No conflicts to report. This was an investigator-initiated study supported by an unrestricted grant from Dermira/Lilly.

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[1]Presented at the American Academy of Dermatology, VMX, April 23-25, 2021
[2]Presented at the Sunscreen Symposium, September 22 - 25, 2021, Orlando, Fl, USA