A Pilot Study of the Safety and Effectiveness of a Novel Device in Subjects With Axillary Hyperhidrosis

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BACKGROUND One-third of U.S. adults are bothered by excessive sweating and 5% suffer from hyperhidrosis, both of which negatively affect quality-of-life (QoL). A single-use disposable patch using the novel targeted alkali thermolysis (TAT) technology is being developed to address this condition.

OBJECTIVE Assess the efficacy and safety of the TAT patch for the treatment of excessive sweating using a randomized, double-blind, sham-controlled study design.

MATERIALS AND METHODS Adults with Hyperhidrosis Disease Severity Scale (HDSS) scores of 3 or 4 ($n = 16$) were treated with an active or sham patch for up to 3 minutes (as established in a previous unpublished feasibility study) and evaluated weekly for 6 weeks post-treatment. The primary effectiveness measure was improved HDSS at Week-4.

RESULTS The study met its objective. For the primary efficacy measure, 83% of TAT-treated subjects reported HDSS scores of 1 or 2 at Week-4 versus 0% of sham-treated subjects ($p = .0032$). Furthermore, 67% of TAT-treated subjects had a 2-point improvement in HDSS scores versus 0% of sham-treated subjects ($p = .0123$). Quality-of-life improvement correlated with HDSS. The TAT patch seemed to be well-tolerated; one transient moderate adverse event that resolved without sequelae was reported.

CONCLUSION The TAT patch successfully demonstrated efficacy and was well-tolerated.

Sweating serves the important function of thermoregulation, for example, keeping the body cool in hot temperatures or during physical activity. But for many people, sweating exceeds this normal function, occurring spontaneously independent of external temperature or exertion and proving recalcitrant to treatment. Approximately 5 percent of the population suffers from the most extreme form of excessive sweating, hyperhidrosis,[1] which may bilaterally affect the axillae, palms, feet, face, or multiple areas.[2] More than 80% of patients report 3 or more focal hyperhidrotic sites.[3] In addition, one-third of U.S. adults say they are bothered by sweating they consider excessive, according to a survey by the International Hyperhidrosis Society.[4] This excessive sweating may be severe enough to impair activities of daily living and cause undue emotional distress. People with hyperhidrosis experience anxiety and depression, may become socially isolated, and suffer a significantly diminished quality-of-life (QoL).[5–7] Despite efforts to control excessive sweating, the severity of hyperhidrosis symptoms does not diminish over time.[3]

Currently available treatments for excessive sweating include topical over-the-counter and prescription antiperspirants; systemic medications; iontophoresis; botulinum toxin injections; energy-based devices such as laser, microwave and focused ultrasound; and thoracic sympathectomy.[2,8,9] Most individuals suffering from excessive sweating report being dissatisfied with available treatment options,[10] many of which are inconvenient or difficult to use and some of which are associated with significant adverse effects.[2,9] Thus, there remains an unmet medical need for effective, well-tolerated, and convenient treatments for axillary hyperhidrosis.

To potentially address this need, the targeted alkali thermolysis (TAT) patch (Candesant Biomedical, San Francisco, CA) was developed. The TAT patch is a noninvasive, nonsystemic novel treatment option currently being studied for excessive sweating or hyperhidrosis of the axillae. In future, the technology could be applied to other areas prone to excessive sweating including hands, face, and feet. The proprietary mechanism of action uses a reaction that produces thermal energy when an alkali metal (M) comes into contact with water (in this case, from sweat glands): $M + H_2O \rightarrow MOH + \frac{1}{2} H_2 + \text{heat}$. Although this is a well-known reaction, to our knowledge, the TAT patch is the first reported clinical application of alkali-metal thermogenesis and is the only patented medical device based on it.[11] More specifically, when applied to clean, dry axilla skin—typically for 3 minutes—the

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adhesive patch delivers TAT to the axillae, directly to the sweat ducts, thereby inactivating sweat glands only where triggered by moisture. Because the thermal energy generated is localized and proportionate to the amount of water (sweat) present, the procedure is selective and potentially most effective on the most active sweat glands.

The current study follows a previous proof-of-concept study (unpublished) that demonstrated the safety, tolerability, and feasibility of the patch in healthy volunteers. The objective of this prospective, randomized, double-blind, sham-controlled study was to assess the safety and efficacy of the TAT patch in subjects with excessive axillary sweating.

Methods

Study Subjects

Adult subjects, 18 to 65 years old, with excessive axillary sweating and gravimetric sweat production (GSP) >40 mg/5 minutes, were enrolled. Other inclusion criteria were a Hyperhidrosis Disease Severity Scale (HDSS)[12] score ≥3. The HDSS is scored from 1 ("My sweating is never noticeable and never interferes with my daily activities") to 4 ("My sweating is intolerable and always interferes with my daily activities") (See **Supplemental Digital Content 1**, Table S1, http://links.lww.com/DSS/B161, which shows the complete HDSS). Subjects also had to be willing to comply with all study procedures. Female subjects of child-bearing potential were required to provide a negative pregnancy test and be willing to use an effective method of birth control during the study.

Reasons for exclusion from the study included history of allergy or sensitivity to any materials used in the study; use of anticholinergic medications, beta-adrenergic blockers, calcium channel blockers, or other systemic treatment that may affect sweat-related symptoms.

Subjects with confirmed eligibility were enrolled and randomized 1:1 to undergo bilateral treatment with the TAT patch or a sham device.

Study Device

The proprietary, investigational TAT patch is comprised of a top layer of nonadhesive polyimide that provides a protective barrier to the device surface (I. Figure 1). The active layer is an alkali metal foil with an adhesive backing. The metal layer is intended to remain in contact with the axilla during treatment and is held in place by the adhesive. The sham patch is identical except it contains no alkali metal. The patch is designed to be applied by a qualified physician and/or trained staff for up to 3 minutes, after which it is removed and discarded.

Study Procedures

The treatment area was established using starch–iodine or hair follicle location. Before treatment, the area was inspected to ensure it was shaved and free of abrasion, broken skin, or other conditions of concern. The axilla was cleaned to ensure it was free of antiperspirant residue, wiped with alcohol and dried so that the skin was free of superficial moisture.

Based on each subject's randomization, the active or the sham patch was then placed on the target area. The patch was removed after 3 minutes or sooner if the subject was uncomfortable; thus, the duration of treatment was partly based on tolerability. Treatment-related discomfort was assessed by the subject using the 10-point Wong-Baker FACES pain scale.[13] Immediately after device removal, the treatment area was cleaned with water and visually inspected by the investigator.

Subjects were contacted by phone 24 to 48 hours post-treatment and queried about any treatment-related pain or adverse events. Subjects were scheduled for weekly office visits for 6 weeks post-treatment; during these visits, assessments included HDSS and GSP, QoL questionnaires, and treatment site inspection.

Study Endpoints

Efficacy was based on changes in HDSS scores (the primary efficacy measure) and GSP values during the 6 weekly post-treatment follow-up evaluations, with Week-4 being the primary time point for evaluation as is customary in other hyperhidrosis studies. Other outcome measures included subject answers to QoL questionnaires. Safety was based on procedure tolerability and absence of severe adverse events attributable to the device.

Statistical Analysis

Because this was a safety and feasibility study, it was not powered to make statistical comparisons between the active treatment and sham cohorts. Comparisons were descriptive in nature, and descriptive statistics were deemed sufficient to demonstrate the potential effectiveness for this pilot study. When appropriate, post hoc statistical analyses were performed to better understand the results.

Ethics

All subjects provided written informed consent before participating in the study. The study protocol and related documents were approved by a commercial investigational review board (Allendale Investigational Review Board of RTA Inc., Old Lyme, CT). The study was conducted in accordance with applicable elements of the International Council on Harmonization E6 Good Clinical Practice Consolidated Guidance,[14] abbreviated requirements of 21 CFR 812.2(b) for nonsignificant risk device studies,[15] and the Declaration of Helsinki, as amended.[16]

Results

The objective of the study was successfully met. Sixteen subjects were enrolled and treated with the TAT patch or sham patch ($n = 8$, 16 axillae in each group); however, one subject was lost to follow-up in each group after the Week-3 visit. Subject demographics and baseline characteristics are summarized in Table 1.

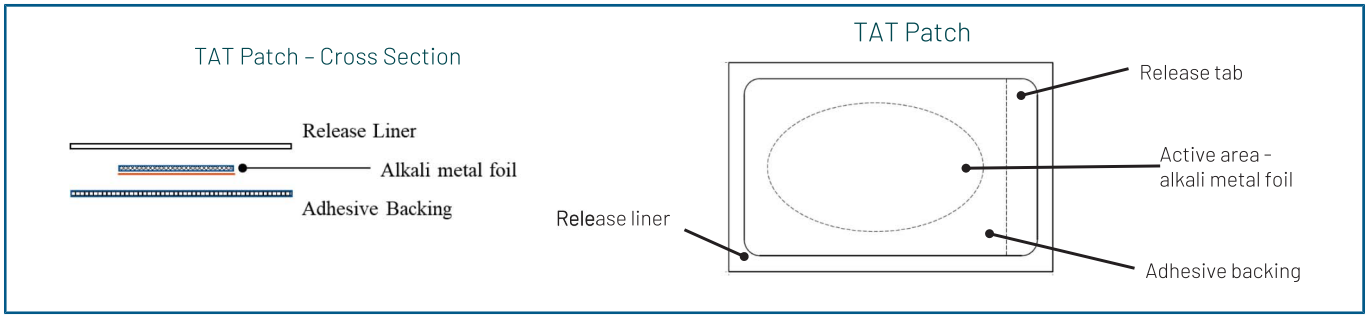

Figure 1. Diagram of the targeted alkali thermolysis patch.

Hyperhidrosis Disease Severity Scale

For the primary efficacy measure at Week-4, 83% of TAT patch subjects reported HDSS scores of 1 or 2 versus 0% of sham-treated subjects. The corresponding percentages at Week-6 were 86% versus 14%, respectively (See **Supplemental Digital Content 2**, Table S2, http://links.lww.com/DSS/B161, which shows the changes in HDSS scores). Although this study was not powered to detect statistical significance, a post hoc analysis (Table 2) found these differences to be significant ($p = .0032$ and $p = .0094$ at Weeks 4 and 6, respectively).

In addition, 67% of TAT patch subjects had a 2-point improvement in HDSS scores at Week 4 versus 0% of sham-treated subjects; the percentages at Week-6 were 71% versus 14%, respectively (See **Supplemental Digital Content 2**, Table S2, http://links.lww.com/DSS/B161, which shows the changes in HDSS scores). A post hoc analysis found these differences to be significant ($p = .0123$ and $p = .0376$ at Weeks 4 and 6, respectively) (Table 2).

Gravimetric Sweat Production

Across the 6-week study, there was a reduction in mean and median GSP in both study groups. The percent change versus baseline in GSP at each weekly visit was calculated for each individual subject, and mean and median percent changes were determined for the 2 treatment groups (See **Supplemental Digital Content 3**, Table S3, http://links.lww.com/DSS/B161), which shows GSP at baseline and Weeks 4

TABLE 1. Subject Demographics

Characteristic, n (%)	TAT Patch	Sham
Female gender	5 (63)	7 (88)
Mean age (SD), yr	37 (11)	29 (10)
Median age (min, max), yr	35 (23, 56)	28 (18, 48)
Race		
White	8 (100)	5 (63)
Black/African American	0	3 (38)
Ethnicity		
Hispanic/Latino	8	6 (75)
Non-Hispanic/Latino	0	2 (25)
Fitzpatrick skin type		
III	0	2 (25)
IV	2 (25)	3 (38)
V	6 (75)	1 (13)
VI	0	2 (25)
HDSS Grade 3	2 (25)	2 (25)
HDSS Grade 4	6 (75)	6 (75)
GSP >40 mg/5 min	8 (100)	8 (100)
Mean GSP (SD), mg/min	78 (28)	148 (84)
Median GSP (min, max), mg/min	71 (43, 138)	144 (50, 299)

GSP, gravimetric sweat production; HDSS, Hyperhidrosis Disease Severity Scale.

TABLE 2. Post Hoc HDSS Analyses			
n/N (%)	**TAT Patch**	**Sham**	**Significance***
Percent of subjects with HDSS Grade 1 or 2			
Week 4	5/6 (83)	0	$p = .0032$
Week 6	6/7 (86)	1/7 (14)	$p = .0094$
Percent of subjects with 2-point improvement			
Week 4	4/6 (67)	0	$p = .0123$
Week 6	5/7 (71)	1/7 (14)	$p = .0376$

* N-1 Chi-squared test.
HDSS, Hyperhidrosis Disease Severity Scale; TAT, Targeted Alkali Thermolysis.

and 6). At Week-6, active-treated subjects demonstrated reductions in mean and median GSP percent changes of 31% and 60%, respectively. Overall, 66.7% of the active treatment subjects experienced a ≥50% reduction in GSP. Sham-treated subjects showed a reduction of 29% in mean and median GSP percent changes, with 14.3% of subjects experiencing a ≥50% GSP reduction.

Quality of Life

As an exploratory endpoint, an additional QoL instrument was used. The instrument assesses QoL on a 5-point scale from 0 to 4, with 4 being extremely bothered or impacted and 0 being not bothered or impacted at all. The overall trends in QoL data were positive, indicating that subjects generally were less affected by their sweating after treatment with the active patch.

At baseline, the mean degree of bother and of impact of aaily activities among the active-treated group (3.13) was similar to the sham-treated subjects (3.63). Among active-treatment subjects, relief in both parameters was apparent as early as the first week after treatment and steadily improved during the study. At Week-4 the differences in bother and impact was statistically significant ($p = .0005$ and $p = .0135$ respectively) By Week-6, the levels of bother and of impact on daily activities were notably less in the active-treated group versus the sham group: 0.71 versus 3.29 and 1.14 versus 3.43, respectively (Figure 2).

Reported sweat-related emotions included embarrassment, frustration, and lack of confidence (See **Supplemental Digital Content 4**, Table S4, http://links.lww.com/DSS/B161, which shows emotions and behaviors in daily life). Behavioral modifications included multiple showers, clothing changes during the day, and avoiding activities or people because of excessive sweating. Consistent with other QoL outcomes, active-treated subjects achieved improvements from baseline measures throughout the follow-up period, whereas there was little change among sham-treated subjects.

An analysis of an emotion/behavior survey that scored its 7 responses as Yes (1) or No (0) showed similar mean baseline scores of 6.13 in the active-treatment group and 6.25 in the sham-treatment group. At the end of the 6-week follow-up period, mean scores were 1.86 and 5.75 in these groups, respectively (See **Supplemental Digital Content 5**, Table S5, http://links.lww.com/DSS/B161, which shows the changes in emotions and behaviors in daily life during the study). Among subjects in the active group, there was a marked improvement in the areas of frustration and lack of confidence because of their sweating at the 4-week and 6-week timepoints.

Procedure Tolerability

Overall, treatment with the active patch was tolerable, because the mean pain score remained below 6 throughout the entire procedure. For most active-treated subjects who reported pain, the pain stopped once the patch was removed and the axilla cleaned; only one subject reported pain that persisted beyond the treatment, and it resolved by the 1-week visit. The mean pain scores were <2 in the sham group, because no heat was generated by the device. One sham-treated subject reported increasing pain, reaching a score of 7 in both axillae, requiring treatment to be stopped. The subject reported no pain immediately after the procedure and the cause of the pain remains unknown.

Safety

One adverse event of bilateral focal redness and swelling occurred in one subject after treatment with the active patch for 3 minutes. The event was of moderate severity and considered treatment related. The subject was treated with silver sulfadiazine cream 1% twice daily and the lesions had largely resolved by Week-2 and completely resolved at the Week-5 visit (the subject missed Week 3 and 4 visits due to vacation). There was no scarring or other sequelae.

Discussion

The objective of this study, the first reported clinical application of alkali-metal thermogenesis, was to assess the safety, tolerability, and efficacy of the novel TAT patch in treating axillary hyperhidrosis. All active-treatment subjects achieved substantial improvements in sweating severity.

Clinical studies of hyperhidrosis typically define treatment success as achieving an HDSS score of 1 or 2 (indicating their sweating was not noticeable or was tolerable, respectively) or improving HDSS scores by ≥2 points.[12] At baseline, all subjects in this study had HDSS scores of 3 or 4. At the end of the 6-week follow-up period,

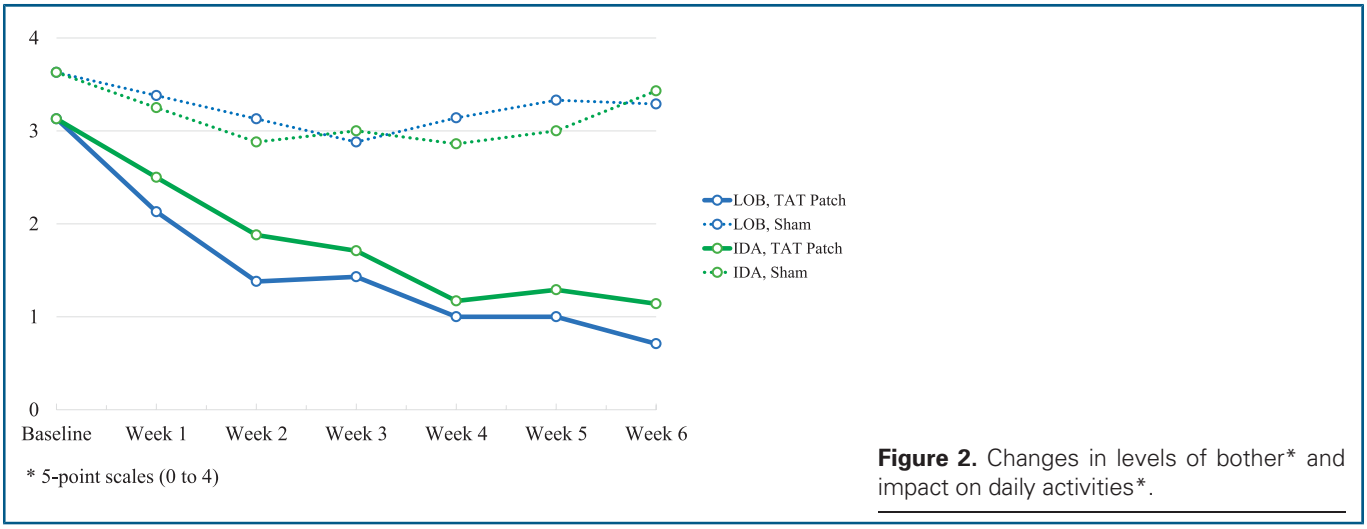

Figure 2. Changes in levels of bother* and impact on daily activities*.

most subjects (86%) treated with the active patch achieved an HDSS score of 1 or 2, indicating that their sweating was not noticeable or was tolerable, respectively. In contrast, only 14% of sham-treated subjects reported similar improvement, suggesting treatment with the active patch provides clinically meaningful improvement. Although the number of subjects in this study was limited, the results compare favorably with existing pharmacological and medical-device treatments.[17,18]

Post hoc analyses compared data from the active-versus sham-treatment groups at the 4-week and 6-week visits. Although this study was not powered to detect statistical significance initially, a statistically significant difference was achieved between the percentage of subjects on the most stringent endpoint used in other products, a ≥2-point improvement in HDSS score in the active group (67%) compared with the sham group (0%) at 4 weeks ($p = .0123$) and 71% versus 14% at 6 weeks ($p = .0376$) (Table 2). In addition, in the most clinically relevant measure (HDSS scores of 1 or 2), highly statistically significant relief from sweating (outcome) was achieved after treatment with the active patch relative to the sham patch at 4 and 6 weeks ($p = .0032$ and $p = .0094$, respectively) after a single treatment.

At Week-6, active-treated subjects demonstrated reductions in mean and median GSP percent changes of 31% and 60%, respectively, compared with 29% (mean and median) for the sham-treated subjects. The comparison of changes in absolute GSP values was complicated by substantial differences between the active-versus sham-patch groups in mean baseline GSP values (78 vs 148 mg/5 min, respectively) and individual GSP values (43–138 vs 50–299 mg/5 minutes) (See **Supplemental Digital Content 3**, Table S3, http://links.lww.com/DSS/B161, which shows GSP at baseline and Weeks 4 and 6), despite similar demographic characteristics and identical HDSS scores, and may be because of a small sample size. This large variation in GSP is not surprising, because many factors influence GSP including diet, emotions, environmental conditions, and medication use,[19] and it has been suggested that GSP is not a good indicator of hyperhidrosis disease severity.[20,21] The data from this study emphasize the need for multiple assessments to confirm treatment effect.[19]

QoL questionnaires assessed the impact of excessive sweating on the daily activities and emotional well-being of each subject. The results consistently demonstrated that subjects treated with the TAT patch enjoyed greater QoL improvement, which correlated with changes in HDSS scores.

The TAT patch was well-tolerated with patients reporting treatment-related discomfort as generally mild and transient. Treatment-related adverse events were limited to bilateral focal redness and swelling ($n = 1$) and pain ($n = 1$).

Conclusion

The TAT patch offers a novel, convenient, and well-tolerated therapy for patients with axillary hyperhidrosis. Subjects suffering the negative effects of excessive sweating can benefit from a new heat-based device that demonstrated safety, clinically meaningful improvements in symptoms, and substantial improvements in QoL. Based on these promising results, further clinical testing is warranted.

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