Efficacy and safety of topical sofpironium bromide gel for the treatment of axillary hyperhidrosis: A phase II, randomized, controlled, double-blinded trial

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Background: Primary axillary hyperhidrosis has limited noninvasive, effective, and well-tolerated treatment options.

Objective: To evaluate the topical treatment of axillary hyperhidrosis with the novel anticholinergic sofpironium bromide.

Methods: A phase II, multicenter, randomized, controlled, double-blinded study. Participants were randomized to 1 of 3 dosages or vehicle, with daily treatment for 42 days. Coprimary end points were the percentage of participants exhibiting ≥1-point improvement in the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) score by logistic regression, and change in HDSM-Ax as a continuous measure by analysis of covariance. Pair-wise comparisons were 1-sided with $\alpha = 0.10$.

Results: At the end of therapy, 70%, 79%, 76%, and 54% of participants in the 5%, 10%, 15%, and vehicle groups exhibited ≥1-point improvement in HDSM-Ax ($P < .05$). Least-square mean (SE) changes in HDSM-Ax were −2.02 (0.14), −2.09 (0.14), 2.10 (0.14), and −1.30 (0.14) (all $P \leq .0001$). Most treatment-related adverse events were mild or moderate.

Limitations: Not powered to detect changes in gravimetric sweat production.

Conclusion: Sofpironium bromide gel produced meaningful reductions in hyperhidrosis severity and had an acceptable safety profile. (J Am Acad Dermatol 2020;82:1321-7.)

Key words: anticholinergic; axillary hyperhidrosis; HDSM-Ax; retrometabolic drug; sofpironium bromide; topical.

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Hyperhidrosis is characterized by sweat production in excess of that needed to maintain thermal homeostasis.[1,2] Estimates of its prevalence have varied widely, but a recent study concluded that hyperhidrosis affects approximately 4.8% of the United States population.[2] Primary hyperhidrosis—not secondary to another medical condition or as an adverse effect of a medication—is almost always bilateral and is limited to specific body regions, such as the axillae, palms, soles, or craniofacial regions, with the axillae the most commonly affected region.[3] Axillary hyperhidrosis can have a profoundly negative effect on quality of life, work, daily activities, social life, and emotional and mental health.[2,4-6]

CAPSULE SUMMARY

- Sofpironium bromide is a rapidly metabolized, retrometabolically designed, anticholinergic drug under investigation for the topical treatment of axillary hyperhidrosis.
- In this phase II dose-finding study, sofpironium bromide elicited sustained reductions in sweating severity and was well-tolerated, suggesting further studies of this drug are warranted.

Primary hyperhidrosis is thought to involve excessive cholinergic stimulation of eccrine sweat glands.[7,8] Accordingly, oral and topical anticholinergic drugs have been used to treat hyperhidrosis.[9-11] The main limitations to their use are systemic anticholinergic effects, although rates are lower with topical agents.[11] Other treatment options include neuromodulators (eg, botulinum toxin injections), iontophoresis, microwave thermolysis, and surgery.[12,13] Despite these treatments, many patients are unsatisfied with current options because of limited or temporary efficacy, adverse effects, invasiveness, or cost.[6]

Sofpironium bromide is an ester analog of glycopyrrolate that inhibits muscarinic receptors, including sweat glands.[14,15] Sofpironium bromide was developed according to the principles of retrometabolic drug design, in which the goal is to develop an active compound that is readily metabolized in vivo to an inactive moiety in a single, predictable reaction.[14,15] This design is expected to reduce systemic effects while maintaining efficacy at the site of application. We conducted a randomized, vehicle-controlled, double-blinded phase II trial to test the efficacy and safety of a topical gel formulation of sofpironium bromide in patients with primary axillary hyperhidrosis.

METHODS

A total of 227 participants were enrolled at 23 experienced clinical trial sites in the United States. The protocol and procedures were approved by the Aspire Institutional Review Board (Santee, CA), and informed consent was obtained from all participants before any study-related procedures. The trial was conducted in accordance with the principles of Good Clinical Practice and the International Council on Harmonisation.

Study design and procedures

Eligible participants were randomly assigned to 1 of 4 study groups: sofpironium bromide gel, 5%, 10%, or 15%, or vehicle (placebo) in a 1:1:1:1 ratio. Randomization was performed by a central administrative center (Sherpa Clinical Packaging, San Diego, CA) using a block size of 8. Participants and investigators were blinded to treatment assignment. Treatment was preceded by a washout period of up to 35 days. Active gels containing sofpironium bromide and vehicle gels were provided in kits containing identical metered-pump containers with the same no-touch applicators. Each kit was labeled with a randomization number. The central administrative center assigned the next available randomization number to each participant in chronologic order. Participants were to apply treatment once daily with a no-touch applicator at bedtime to both axillae for 42 days and to use 1 full pump actuation, approximately 0.56 g (0.67 mL) of gel, per axilla.

The primary efficacy end point was change in the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) score. The HDSM-Ax is a validated, 11-item, patient-reported measure of symptom severity and frequency intended for use in patients aged ≥12 years.[16] It was developed to address concerns that existing measures failed to meet United States Food and Drug Administration requirements and had limitations in sensitivity for detecting changes in symptom severity and frequency. HDSM-Ax satisfies regulatory guidance and scientific criteria as a fit-for-purpose, validated measure of axillary hyperhidrosis symptom severity and frequency.[17] Each HDSM-Ax question has 5 response options ranging from 0 (no sweating) to 4 (worst possible sweating). The overall HDSM-Ax score is expressed as the average of the 11 item scores. Secondary and exploratory efficacy end points included the changes from baseline in gravimetric sweat production (GSP), Hyperhidrosis Disease Severity Score (HDSS), and modified Dermatology Life Quality Index (DLQI).

All efficacy assessments were performed at baseline and at prespecified clinic visits on days 8, 15, 22, 29, 36, 41, 42, 43, and 57, with the exception of the

Abbreviations used:

ANCOVA:	analysis of covariance
DLQI:	Dermatology Life Quality Index
EOT:	end of treatment
GSP:	gravimetric sweat production
HDSM-Ax:	Hyperhidrosis Disease Severity Measure-Axillary
HDSS:	Hyperhidrosis Disease Severity Score

DLQI, which was performed at baseline and day 43. Baseline values for HDSM-Ax and HDSS were defined as the average of measurements from the first and last screening visits, and end-of-treatment (EOT) values were defined as the average of measurements obtained at days 41, 42, and 43. The baseline value for GSP was defined as the median of 3 pretreatment measurements, and the EOT value was the median of measurements at days 41, 42, and 43.

Vital signs, tolerability, and adverse events were evaluated at each visit. Tolerability assessments included assessments of burning, itching, dryness, scaling, and erythema using standardized 5-point scales from 0 (absent) to 4 (severe). Laboratory tests included routine hematology and chemistry analysis and urinalysis.

Participants

Participants were adults (≥18 years old) in good general health with a diagnosis of primary axillary hyperhidrosis, an HDSM-Ax score of ≥3, and an HDSS score of 3 or 4. In addition, participants had to exhibit GSP >50 mg/5 min at rest in each axilla, and at least 150 mg/5 min total for both axillae at room temperature (20°-25°C). Participants were required to have had symptoms of axillary hyperhidrosis for 6 months before study entry. Patients were excluded if they had skin or subcutaneous conditions in either axilla other than hyperhidrosis or had received any procedures or treatments that could interfere with study drug activity or metabolism. Women of childbearing potential were required to use reliable forms of contraception such as abstinence, having a sterile partner, hormonal contraception, intrauterine devices, or barrier methods.

Statistical analysis

A sample size of 50 evaluable participants per group was targeted to provide 87% power for detecting a 1-sided $P < .10$ difference between an active treatment group and the placebo group, with the assumption that the response rates (percentage of participants exhibiting ≥1-point improvement in HDSM-Ax score) were 75% and 50%, respectively. As a phase II, signal-seeking trial, a 1-sided $P < .10$ was chosen as the threshold for a statistically meaningful signal. Unless otherwise specified, all P values are 1-sided. The primary analyses of efficacy were performed using the modified intent-to-treat population, which included all participants who were randomized and dispensed the study drug. For efficacy analyses, participants were analyzed according to their randomized treatment assignment.

According to the protocol, the primary efficacy end point was analyzed as a binary outcome (≥1-point improvement or not) and also as a continuous measure. For the binary analysis, a logistic regression was performed with treatment assignment and baseline HDSM-Ax score as independent variables. Any participant with response status unknown between baseline and EOT was considered a nonresponder. For analysis of HDSM-Ax as a continuous measure, changes in HDSM-Ax scores from baseline to EOT were compared between each active group and placebo by an analysis of covariance (ANCOVA) adjusted for the baseline HDSM-Ax score.

To prevent the study's overall false-positive rate from exceeding 0.10 during the multiple between-group comparisons, analyses were performed using a gate-keeping hierarchy. The 15% sofpironium bromide group was first compared with the vehicle group, followed by the 10% and 5% sofpironium bromide groups in a stepwise fashion only when the preceding analysis was positive. Supportive mixed-model repeated-measures analyses were performed using all available HDSM-Ax change-from-baseline data on study days 8, 15, 22, 29, and 36 and at EOT for the binary and continuous data.

GSP is difficult to measure reliably and has high variability. Therefore, and to reduce any potential influence of outliers, 2 analytic methods were prespecified for evaluating GSP. First, continuous GSP data were analyzed for change from baseline. Second, the continuous data were transformed into ranks across the 4 treatment groups, and the ranks were analyzed. Both analyses were performed by ANCOVA with baseline as a covariate.

Response rates were also analyzed according to 2 sets of composite response criteria: response was defined as ≥50% reduction in GSP and a ≥1- or ≥2-point improvement in HDSM-Ax. Results were analyzed by ANCOVA.

Other secondary and exploratory end points included HDSS response status (with response defined as a 1- or a 2-point improvement from baseline to EOT) and change from baseline to EOT (day 43) in DLQI. Response percentages were analyzed for HDSS; DLQI was analyzed using an ANCOVA model adjusted for baseline score.

Table I. Baseline and demographic characteristics and participant disposition

Variable	Vehicle	Sofpironium bromide 5%	Sofpironium bromide 10%	Sofpironium bromide 15%
Total randomized, No.	57	57	57	56
Study medication not dispensed, No. (%)	0	0	0	2 (4)
Safety* and mITT† populations, No.	57	57	57	54
Age, mean (SD), y	30.0 (8.6)	30.8 (10.2)	33.7 (11.3)	30.7 (9.2)
Female, No. (%)	30 (53)	25 (44)	22 (39)	25 (46)
Race/ethnicity				
Hispanic or Latino, No. (%)	13 (23)	8 (14)	12 (21)	15 (28)
Black or African American, No. (%)	13 (23)	6 (11)	9 (16)	10 (19)
White, No. (%)	43 (75)	59 (86)	45 (79)	42 (78)
Time since symptom onset, mean (SD), mo	180 (105)	197 (133)	220 (152)	187 (111)
Baseline characteristics of mITT population				
HDSM-Ax score, mean (SD)	3.39 (0.29)	3.49 (0.32)	3.50 (0.29)	3.57 (0.31)
GSP, mean (SD), mg/5 min	279.4 (178.8)	274.3 (191.4)	288.5 (195.6)	311.1 (187.2)
Discontinued during treatment, No. (%)	5 (9)	7 (12)	8 (14)	9 (17)
Primary reason for discontinuation, No. (%)				
Adverse event, No. (%)	0	1 (2)	4 (7)	7 (13)
Participant withdrawal	3 (5)	3 (5)	1 (2)	0
Other	2 (4)	2 (4)	3 (5)	2 (4)
Lack of efficacy	0	1 (2)	0	0
Completed study, No. (%)	52 (91)	50 (88)	49 (86)	45 (83)

GSP, Gravimetric sweat production; *HDSM-Ax*, Hyperhidrosis Disease Severity Measure-Axillary; *mITT*, modified intent-to-treat; *No.*, number.
*Safety population includes all participants randomized in the study who received the study drug at least once. For the safety analysis, participants were included in the group that corresponded to the treatment they received. All participants in the safety populations received treatment corresponding to their randomized allocation.
†The mITT population includes all participants who were randomized and dispensed the study drug. For analyses, participants were included in the group into which they were randomized.

RESULTS

There were 227 participants in the trial. Two participants initially randomized to the sofpironium bromide gel 15% group were withdrawn before the study drug was dispensed because they did not meet eligibility criteria at the pretreatment visit. The withdrawals were performed without knowledge of the randomized treatment assignment. The remaining 225 participants constituted the safety and modified intent-to-treat populations (see Methods). Enrollment and all trial procedures were performed between January 2016 and September 2017. Baseline and demographic characteristics and participant disposition are summarized in Table I. The demographics of the groups were similar, and participants had experienced symptoms of axillary hyperhidrosis for an average of 15 to 18 years.

Efficacy

Coprimary end point analyses of HDSM-Ax. After the hierarchical testing procedure (see Methods), statistically significant improvements in HDSM-Ax from baseline to EOT were observed for each sofpironium bromide group compared with the vehicle group in the binary and continuous analyses. For the binary analysis, a significantly higher percentage of participants in each sofpironium bromide group exhibited ≥1- or ≥2-point improvement in HDSM-Ax from baseline to EOT vs the vehicle group (Fig 1, *A*). Changes from baseline to each clinic visit for mean HDSM-Ax score are shown in Fig 1, *B*. Clinically meaningful differences were observed at the first clinic visit (day 8) and were sustained for the duration of the treatment period. At EOT, mean (SE) changes from baseline in HDSM-Ax score in the 5%, 10%, and 15% sofpironium bromide groups, respectively, were −2.02 (0.14), −2.09 (0.14), and −2.10 (0.14). The change from baseline to EOT in the vehicle group was −1.30 (0.14). All changes from baseline to EOT in the sofpironium bromide groups for continuous data analyses demonstrated statistically significant difference from the vehicle group (1-sided $P \leq .0001$). After cessation of treatment (day 57, approximately 2 weeks after the last dose), HDSM-Ax scores for all active-treatment groups trended toward the vehicle group. Mixed-model repeated-measures analyses using both the binary and continuous HDSM-Ax data yielded results that were qualitatively similar to the primary analyses.

Secondary efficacy end point: GSP. When GSP was measured as a continuous variable, all dose groups of sofpironium bromide gel exhibited

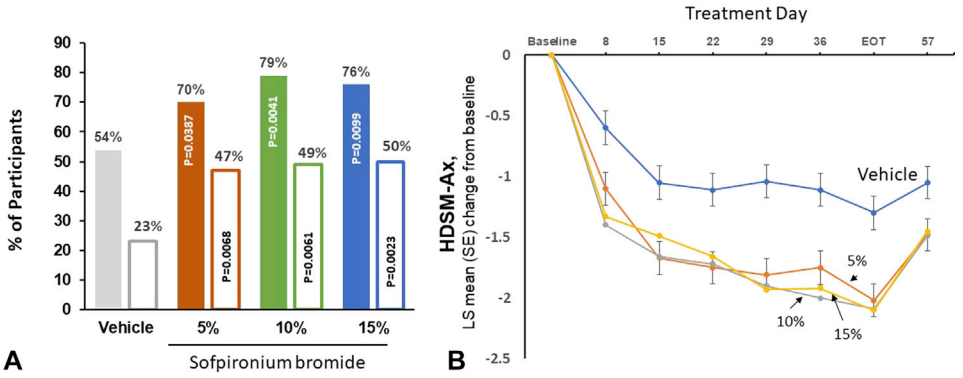

Fig 1. (**A**) Percentage of participants exhibiting ≥1-point improvement (*filled bars*) or ≥2-point improvement (*open bars*) from baseline in the Hyperhidrosis Disease Severity Measure-Axillary (*HDSM-Ax*) at the end of treatment. (**B**) Least-square (*LS*) mean (SE) change from baseline in HDSM-Ax during the treatment phase and approximately 2 weeks after cessation of active treatment (day 57). SEs for the 10% and 15% sofpironium bromide groups (not shown for visual clarity) were of similar magnitude as for the 5% group.

Table II. Other secondary and exploratory end points

Variable	Vehicle (n = 57)	Sofpironium bromide 5% (n = 57)	*P*	10% (n = 57)	*P*	15% (n = 54)	*P*
Composite response, No. (%)							
≥1-point improvement in HDSM-Ax and ≥50% reduction in GSP (baseline to EOT)	22 (39)	34 (60)	.0154	29 (51)	.1447	32 (59)	.0181
≥2-point improvement in HDSM-Ax and ≥50% reduction in GSP (baseline to EOT)	10 (18)	22 (39)	.0122	19 (33)	.0531	25 (46)	.0014
Hyperhidrosis Disease Severity Scale, No. (%)							
≥1-point improvement (baseline to EOT)	29 (51)	42 (74)	.0079	39 (68)	.0499	39 (72)	.0139
≥2-point improvement (baseline to EOT)	4 (7)	21 (37)	.0006	20 (35)	.0021	17 (32)	.0052
Dermatology Life Quality Index							
Change from baseline to EOT, mean (SD)	−5.9 (5.4)	−9.1 (6.2)	.0009	−8.6 (6.2)	.0035	−10.1 (6.7)	<.0001

EOT, End of treatment; *GSP*, gravimetric sweat production; *HDSM-Ax*, Hyperhidrosis Disease Severity Measure-Axillary; *No.*, number.

a greater mean reduction from baseline to EOT compared with vehicle; however, only the 15% sofpironium bromide group met the prespecified criterion for a meaningful positive signal vs the vehicle group (1-sided P = .0644). Least-square mean differences (95% confidence interval) from the vehicle group for the 5%, 10%, and 15% sofpironium bromide groups, respectively, were −12.1 mg (−61.7 to 37.6), −16.8 mg (−66.9 to 33.4), and −39.6 mg (−90.7 to 11.6). For the rank-transformed GSP data, the 5% and 15% sofpironium bromide groups both had meaningful GSP improvements over the vehicle group. The P values (1-sided) comparing the 5%, 10%, and 15% dose groups to vehicle were 0.01, 0.31, 0.04, respectively.

Additional secondary end points. Two different HDSM-Ax and GSP composite response criteria were investigated, each based on changes from baseline to EOT. The percentages of participants satisfying each set of criteria are reported in Table II. All sofpironium bromide groups had meaningfully higher response rates than the vehicle group except for the 10% sofpironium bromide group evaluated by the least stringent composite response criterion. Results of other secondary end points are reported in Table II. More participants in the sofpironium bromide groups exhibited ≥1- or ≥2-point improvements in HDSS compared with the vehicle group. The 3 sofpironium groups exhibited meaningfully greater mean improvements in DLQI scores compared with the vehicle group.

Safety and tolerability

A safety summary is reported in Table III. Among 225 participants in the safety population, 73 reported 177 treatment-emergent adverse events (TEAEs), of which 104 (in 51 participants) were considered to be possibly, probably, or definitely related to the study treatment. One serious TEAE (myocardial infarction) occurred in the 5% sofpironium bromide group but

Table III. Summary of safety

Variable	Vehicle (n = 57)	Sofpironium bromide 5% (n = 57)	Sofpironium bromide 10% (n = 57)	Sofpironium bromide 15% (n = 54)
Participants reporting ≥1 TEAE, No. (%)	9 (16)	17 (30)	19 (33)	28 (52)
TEAEs, No. (%)*				
Serious TEAEs, No. (%)	0	1 (2)	0	0
TEAEs graded as "severe"	0	2 (4)	2 (4)	4 (7)
TEAEs determined by investigator to be related to study drug	2 (4)	12 (21)	17 (30)	20 (37)
TEAEs leading to discontinuation	0	1 (2)	4 (7)	7 (13)
Deaths	0	0	0	0
TEAEs occurring in ≥2 participants†				
Gastrointestinal disorders				
Dry mouth	1 (2)	9 (16)	9 (16)	12 (22)
General disorders and administration site conditions				
Application site pain	0	1 (2)	3 (5)	5 (9)
Application site pruritus	0	0	3 (5)	3 (6)
Application site dermatitis	0	3 (5)	1 (2)	0
Eye disorders				
Vision blurred	0	2 (4)	6 (11)	5 (9)
Dry eye	0	2 (4)	2 (4)	1 (2)
Mydriasis	0	0	1 (2)	1 (2)
Infections and infestations				
Nasopharyngitis	0	3 (5)	1 (2)	3 (6)
Renal and urinary disorders				
Urinary hesitation	0	0	2 (4)	4 (7)
Local tolerability assessments, No. (%)‡				
Any local symptoms				
Any severity	33 (58)	40 (70)	36 (63)	36 (67)
Worst reported severity				
Minimal/mild	29 (51)	29 (51)	23 (40)	18 (33)
Moderate	4 (7)	11 (19)	9 (16)	16 (30)
Severe	0	0	4 (7)	2 (4)
Burning§				
Any severity	23 (40)	24 (42)	27 (47)	26 (48)
Minimal/mild	20 (35)	20 (35)	22 (39)	14 (26)
Moderate	3 (5)	4 (7)	2 (4)	10 (19)
Severe	0	0	3 (5)	2 (4)
Itching§				
Any severity	21 (37)	22 (39)	21 (37)	22 (41)
Minimal/mild	20 (35)	18 (32)	15 (26)	11 (20)
Moderate	1 (2)	4 (7)	4 (7)	9 (17)
Severe	0	0	2 (4)	2 (4)
Dryness‖				
Any severity	6 (11)	16 (28)	21 (37)	18 (33)
Minimal/mild	6 (11)	13 (23)	16 (28)	15 (28)
Moderate	0	3 (5)	5 (9)	3 (6)
Severe	0	0	0	0
Erythema‖				
Any severity	16 (28)	28 (49)	27 (47)	30 (56)
Minimal/mild	15 (26)	21 (37)	19 (33)	24 (44)
Moderate	1 (2)	7 (12)	6 (11)	6 (11)
Severe	0	0	2 (4)	0
Scaling‖				
Any severity	2 (4)	10 (18)	17 (30)	15 (28)
Minimal/mild	2 (4)	8 (14)	13 (23)	12 (22)
Moderate	0	2 (4)	4 (7)	3 (6)
Severe	0	0	0	0

TEAE, Treatment-emergent adverse event.

*Participants reporting >1 occurrence of the same TEAE were counted only once using the closest relationship to study drug.

†Participants in any treatment group according to Medical Dictionary for Regulatory Activities System Organ Class/Preferred Term.

‡Local tolerability signs and symptoms that resulted in a participant requiring a concomitant therapy, interruption of treatment, or discontinuation from the study were reported as an adverse event.

§Assessed by participants.

‖Assessed by investigators.

was not considered related to the study drug. Most TEAEs were mild or moderate in intensity and all resolved after treatment cessation. Eight TEAEs were graded as severe in intensity and were typical of anticholinergic symptoms (dry mouth and blurred vision) or associated with the application site, except for 1 severe TEAE of bacterial osteomyelitis that was unrelated to the study drug.

TEAEs resulted in 12 participants discontinuing from the study (Table III), and all were typical symptoms of anticholinergic drugs (blurred vision, dry mouth, mydriasis, urinary hesitation, constipation, dry eye) or related to the application site (burning, itching, dryness, scaling or erythema). Local site reactions specifically evaluated by the investigator (erythema, dryness, and scaling) or reported by participants (burning and itching) were more common in the sofpironium bromide-treated groups than the vehicle-treated group (Table II). There were no apparent differences between the sofpironium bromide groups and vehicle group in laboratory results or vital signs.

DISCUSSION

The novel anticholinergic drug sofpironium bromide, applied to the axillae in a topical gel

formulation containing 5%, 10%, or 15% active drug, induced clinically significant and statistically meaningful reductions in hyperhidrosis severity according to 3 patient-reported outcome measures. Although the vehicle group exhibited notable improvements in HDSM-Ax, as has been observed in other hyperhidrosis treatment trials using patient-reported outcomes,[11] the active-treatment groups exhibited clinically meaningful differences relative to placebo. Those differences were observed as early as the first postbaseline visit on day 8, and the differences were sustained during the treatment period. The patient-reported efficacy end points did not exhibit dose-dependence within the dose range studied. Adverse events were mostly consistent with expected anticholinergic actions. Safety and tolerability end points exhibited dose-related trends. Across all dosage groups, most adverse events were mild or moderate in intensity and all resolved by study end.

GSP is known to have wide variability and poor correlation with patient-reported outcomes.[18] Therefore, the current phase II study was not designed to detect treatment differences in GSP. Nevertheless, the 15% sofpironium bromide gel demonstrated a statistically significant result over vehicle when GSP was analyzed as a continuous variable, and the 5% and 15% concentrations both demonstrated an advantage over vehicle when GSP was analyzed on the rank scale. For both HDSM-Ax and GSP, minor baseline imbalances between treatment arms were accounted for by the inclusion of baseline values in the primary ANCOVA models.

We also evaluated 2 secondary end points based on composite response criteria incorporating changes in the HDSM-Ax score and changes in GSP. Both end points demonstrated clinically meaningful differences between the sofpironium bromide groups and the vehicle group, although the response rate in the 10% sofpironium group was not statistically different from the vehicle group for the least stringent response criterion. The results of this phase II trial of topical sofpironium bromide gel for treatment of primary axillary hyperhidrosis will require confirmation in further trials.

CONCLUSIONS

In this phase II trial, topically applied sofpironium bromide gel, at concentrations of 5%, 10%, and 15%, reduced axillary hyperhidrosis severity as demonstrated by improvement in HDSM-Ax, HDSS, and DLQI. Composite response criteria with thresholds for decrease in HDSM-Ax and GSP were supportive. Sofpironium bromide gel had a safety and tolerability profile suitable for further study in phase III trials.

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