Sofpironium Targets M3 Receptors and Results in Early Clinical Meaningful Improvement in Primary Axillary Hyperhidrosis (PAH)

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SYNOPSIS

- Muscarinic receptors M1–M5 are present in various body regions; M3 is the primary muscarinic receptor in eccrine sweat glands[1] (**Figure 1**)
- In primary axillary hyperhidrosis (PAH), sweat glands are overstimulated by acetylcholine binding to M3 receptors, triggering excessive sweat[2,3]
- Sofpironium topical gel, 12.45% is a first-in-class, topical anticholinergic (Ach) FDA approved for treatment of PAH in persons ≥9 years[4,5]
- Sofpironium was retrometabolically designed to optimize efficacy and minimize Ach side effects[6-8] (**Figure 2**)
- *In vitro* data supports the mechanism by which sofpironium likely exerts its early and clinically meaningful axilla sweat reduction through M3 receptor selectivity[9-12]

Figure 1. Muscarinic Receptors Description[1-3]

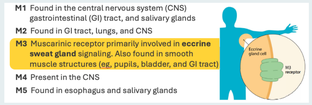
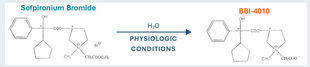


Figure 2. Sofpironium Bromide[5-8]



OBJECTIVES

- To describe the likely mechanism of action of sofpironium through targeting of the M3 receptor
- To report the observed efficacy of sofpironium topical gel, 12.45% over time in terms of subjects achieving ≥1-point improvement and ≥2-point improvement in HDSM-Ax-7 and 70% reduction in GSP
- To identify the cumulative treatment-related adverse events (TEAEs) observed from baseline to end of treatment (EOT) in 2 pivotal phase 3 studies, including local site reactions, Ach TEAEs, and degree of severity

METHODS

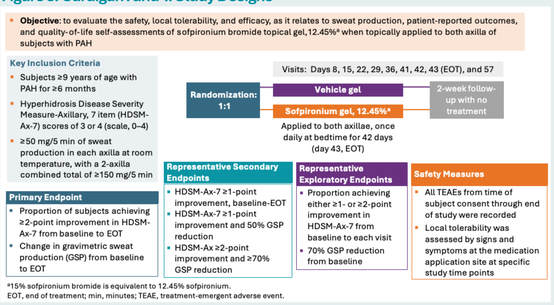
In Vitro Pharmacology[10-12]

- Radioligand binding assay study with 4 groups was used to determine the potency of test substance required to inhibit human muscarinic receptors
  - Sofpironium; sofpironium (2R, 3R, 1R); sofpironium (2R, 3R, 1S); glycopyrrolate
- Half maximal inhibitory concentration (IC_{50}) values determined by non-linear least-squares regression analysis; K_i values represent binding affinity (i.e., a smaller number indicates a greater binding affinity and less test substance needed to inhibit receptor)

Cardigan I and Cardigan II Studies[13-15]

- Two identical multicenter, randomized, vehicle-controlled, double-blinded, parallel-groups, phase 3 studies to evaluate the efficacy and safety of sofpironium gel, 12.45% once daily for the treatment of PAH (**Figure 3**)[9-11]

Figure 3. Cardigan I and II Study Designs[13-15]



[a]15% sofpironium bromide is equivalent to 12.45% sofpironium.
EOT, end of treatment; min, minutes; TEAE, treatment-emergent adverse event.

RESULTS

In Vitro Pharmacology[9-12]

Radioligand binding assay results (**Table 1**)

- Sofpironium achieved ≥50% inhibition at 10 nM for M3 receptors and 100 nM for M1, M2, M4, M5; glycopyrrolate achieved ≥50% inhibition at 1 nM for M1-M5[10,12]
- Results for sofpironium isotope variants were similar (data not shown)[10,12]
- Glycopyrrolate appeared more potent but did not demonstrate M3 receptor selectivity; sofpironium had ~10 times greater selectivity for the M3[11]

These *in vitro* data support the mechanism by which sofpironium reduces sweat through targeting of M3 receptors (**Figure 4**)

Figure 4. M3 Receptor Blockage With Sofpironium Topical Application

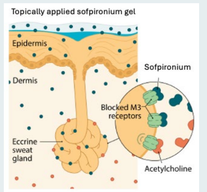


Table 1. Radioligand Binding Assay Results

Muscarinic Receptor	Concentration	% Inhibition	IC_{50} Inhibition	K_i Binding Affinity
Sofpironium				
M1	100 nM	74%	36.3 nM	8.91 nM
M2	100 nM	71%	39.2 nM	16.5 nM
M3	10 nM	55%	7.96 nM	3.85 nM
M4	100 nM	76%	36.4 nM	7.85 nM
M5	100 nM	89%	15.1 nM	9.33 nM
Glycopyrrolate				
M1	1 nM	83%	0.241 nM	0.0590 nM
M2	1 nM	74%	0.314 nM	0.132 nM
M3	1 nM	86%	0.201 nM	0.0973 nM
M4	1 nM	80%	0.251 nM	0.0541 nM
M5	1 nM	74%	0.396 nM	0.245 nM

Cardigan I and II Studies[13-15]

Baseline demographic characteristics were similar in vehicle and sofpironium groups in both studies

Table 2. Cardigan I and II Baseline Demographic and Clinical Characteristics (ITT Population)[14,15]

Characteristic	Cardigan I		Cardigan II	
	Vehicle (N=177)	Sofpironium (N=173)	Vehicle (N=171)	Sofpironium (N=180)
Sex, n (%)				
Female	99 (55.9)	98 (56.6)	103 (60.2)	92 (51.1)
Male	78 (44.1)	75 (43.4)	68 (39.8)	88 (48.9)
Age, mean ± SD (min, max)	32.4 ± 10.9 (14, 71)	32.9 ± 11.6 (11, 64)	31.7 ± 11.1 (11, 69)	32.1 ± 12.2 (10, 76)
Race, n (%)				
White	132 (74.6)	142 (82.1)	135 (78.9)	143 (79.4)
Black or African American	44 (24.9)	32 (18.5)	35 (20.5)	34 (18.9)
Time since onset of PAH symptoms (months), mean ± SD	184.4 ± 116.9	179.3 ± 115.2	194.4 ± 117.3	202.6 ± 131.9
Baseline HDSM-Ax-7 scores (0–4), mean ± SD	3.55 ± 0.32	3.51 ± 0.33	3.57 ± 0.33	3.60 ± 0.32

HDSM-Ax-7: Patient-reported Outcome Measure[13-17]

- 7 questions address the most frequently mentioned daily concerns that impact PAH patients; scored from 0 to 4 where 4 represents the most severe experience
- Validated measure that meets regulatory and scientific requirements for content validity, psychometric performance, and clinical meaningfulness

Question 1
Since you woke up yesterday, how severe was your experience with underarm sweating when you felt nervous, stressed or anxious?

Question 2
Since you woke up yesterday, how severe was your experience with damp or wet clothing?

Question 3
Since you woke up yesterday, how severe was your experience with underarm sweating after little or no physical exercise?

Question 4
Since you woke up yesterday, how severe was your experience with underarm wetness?

Question 5
Since you woke up yesterday, how severe was your experience with underarm sweating for no apparent reason?

Question 6
Since you woke up yesterday, how severe was your experience with underarm sweating that was unmanageable?

Question 7
Since you woke up yesterday, how severe was your experience with underarm sweating when you were cool?

Response Options
0 – I did not experience this
1 – Mild
2 – Moderate
3 – Severe
4 – Very Severe

RESULTS (continued):

More sofpironium subjects achieved HDSM-AX-7 ≥1- and ≥2-point improvements vs. vehicle beginning at day 8 through EOT (**Figures 5a,b; 6a,b**). A higher proportion of sofpironium subjects achieved statistically significant GSP changes from baseline-EOT. More sofpironium subjects achieved ≥70% GSP reduction from baseline-EOT (**Figure 7**).

Figure 5a. Cardigan I Subjects Achieving ≥1-point Improvement in HDSM-Ax-7 (ITT)

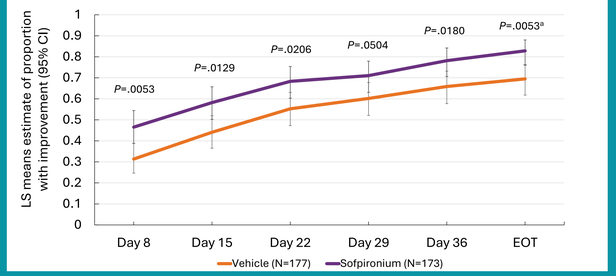


Figure 5b. Cardigan II Subjects Achieving ≥1-point Improvement in HDSM-Ax-7 (ITT)

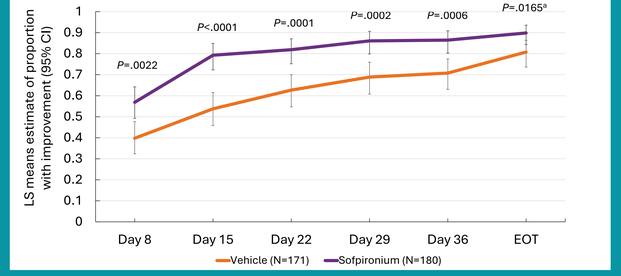


Figure 7. Cardigan I and Cardigan II Subjects Achieving ≥70% Reduction in GSP (Pooled ITT)

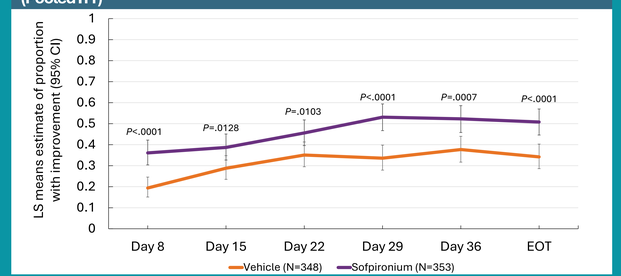


Figure 6a. Cardigan I Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 (ITT)

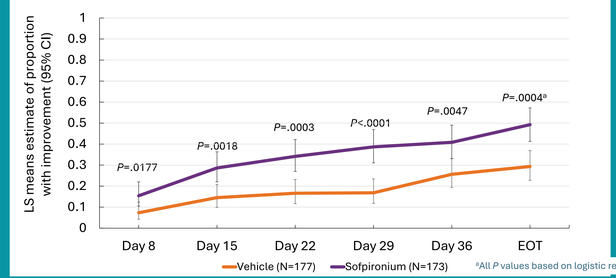
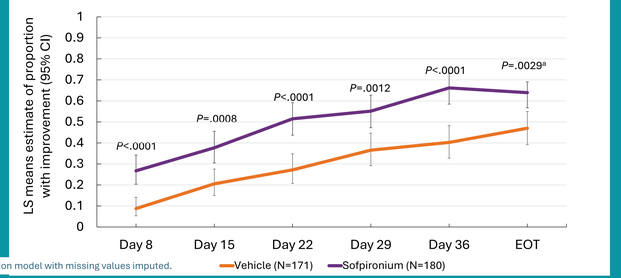


Figure 6b. Cardigan II Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 (ITT)



[a]All *P* values based on logistic regression model with missing values imputed.

CONCLUSIONS

- Sofpironium topical gel, 12.45% is the first new chemical entity FDA approved for the treatment of PAH in people ≥9 years[4,5]
- Sofpironium likely exerts its sweat-reducing effect through highly selective targeting of the M3 receptor as demonstrated *in vitro*[9-12]
- Sustained efficacy and rapid onset of action of sofpironium were demonstrated in the 2 pivotal phase 3 trials, with more sofpironium treated subjects achieving ≥1- and ≥2-point improvements in the HDSM-Ax-7 at EOT, and over time, vs. vehicle, with improvements seen as early as day 8[13-15]
- Achieving ≥1-point improvement in the HDSM-Ax is considered clinically meaningful[17]
- A higher proportion of sofpironium subjects achieved statistically significant GSP changes from baseline-EOT vs. vehicle[13-15]
- More sofpironium subjects achieved ≥70% GSP reduction from baseline-EOT, and at each visit, vs. vehicle[14,15]
- Sofpironium was generally well tolerated; most TEAEs, including Ach and local site reaction TEAEs, were mild or moderate in severity and transient[13-15]

Safety

Table 3. Cardigan I and II Cumulative TEAEs (Safety Population)[14-15]

Cumulative TEAEs up to Day 43/EOT, n (%) mild | moderate | severe	Cardigan I		Cardigan II	
	Vehicle (N=176)	Sofpironium (N=173)	Vehicle (N=171)	Sofpironium (N=180)
Any TEAE	20 (11.4) 18 (10.2) | 2 (1.1) | 0	58 (33.5) 32 (18.5) | 23 (13.3) | 3 (1.7)[a]	20 (11.7) 13 (7.6) | 7 (4.1) | 0	80 (44.4) 37 (20.6) | 38 (21.1) | 5 (2.8)[b]
Any local site reaction TEAE	6 (3.4) 5 (2.8) | 1 (0.6) | 0	33 (19.1) 15 (8.7) | 15 (8.7) | 3 (1.7)	4 (2.3) 3 (1.8) | 1 (0.6) | 0	39 (21.7) 17 (9.4) | 21 (11.7) | 1 (0.6)
Any anticholinergic TEAE	0	30 (17.3) 18 (10.4) | 12 (6.9) | 0	3 (1.8) 3 (1.8) | 0 | 0	42 (23.3) 21 (11.7) | 18 (10.0) | 3 (1.7)
Eye disorders	0	22 (12.7) 12 (6.9) | 10 (5.8) | 0	1 (0.6) 1 (0.6) | 0 | 0	34 (18.9) 17 (9.4) | 16 (8.9) | 1 (0.6)
Mydriasis	0	13 (7.5) 7 (4.0) | 6 (3.5) | 0	0	9 (5.0) 2 (1.1) | 7 (3.9) | 0
Vision blurred	0	9 (5.2) 5 (2.9) | 4 (2.3) | 0	1 (0.6) 1 (0.6) | 0 | 0	21 (11.7) 11 (6.1) 9 (5.0) | 1 (0.6)
Dry eye	0	1 (0.6) 1 (0.6) | 0 | 0	0	6 (3.3) 5 (2.8) | 0 | 1 (0.6)
Dry mouth	0	20 (11.6) 17 (9.8) | 3 (1.7) | 0	2 (1.2) 2 (1.2) | 0 | 0	31 (17.2) 24 (13.3) | 4 (2.2) | 3 (1.7)
Urinary retention	0	2 (1.2) 0 | 2 (1.2) | 0	0	6 (3.3) 3 (1.7) | 3 (1.7) | 0
Discontinuations due to any TEAE	0	5 (2.9)	0	9 (5.0)

[a] Cardigan I: The 3 subjects who experienced severe TEAEs were application site pain in 3 subjects (1.7%) and application site pruritus in 1 subject (0.6%).
[b] Cardigan II: The 5 subjects who experienced severe TEAEs were dry mouth in 3 subjects (1.7%), dry eye, vision blurred, application site reaction, fibula fracture, and foot fracture (1 subject [0.6%] each)

DISCLOSURES

Botanix Pharmaceuticals ("Botanix") funded the studies, poster development, and medical writing services provided by Dana Randall, MS, PharmD. Dr. Del Rosso was an investigator and is consultant to Botanix. Dr. Hebert was an investigator and received research grants paid to the McGovern School of Medicine. Dr. Cartwright is an employee of Botanix. Dr. Walker is the former Chief Medical Advisor at Botanix and is currently a member of the Board of Directors of Botanix.

References 1. Broadley K, Kelly D. *Molecules.* 2001;6(3):142-193. **2.** Cui C, et al. *Exp Dermatol.* 2015;24(9):644-650. **3.** Coon EA and Low PA. Regulation of sweating. In *Primer on the Autonomic Nervous System, Fourth Edition.* 2022: pages 253-256. Elsevier; https://doi.org/10.1016/B978-0-323-85492-4.00079-X. **4.** Novel drug: US FDA. Novel drug approvals for 2024. https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024. Published July 14, 2025. Accessed July 10, 2025. **5.** Sofdra™ (sofpironium) topical gel, 12.45% [prescribing information]. Phoenix, AZ: Botanix SB Inc. July 2025. Accessed September 23, 2025. https://www.sofdra.com/pdfs/prescribing-information.pdf. **6.** Bodor N, Friedman A, Smith S. Investigating treatment of primary axillary hyperhidrosis with a topical retrometabolic anticholinergic drug. Poster presented at: Fall Clinical 2021; October 2021; Las Vegas, NV. **7.** Gregoriou S, et al. *Expert Opin Investig Drugs.* 2022;31(1):15-21. **8.** National Center for Biotechnology Information. PubChem Compound Summary for CID 86301316, Sofpironium bromide. https://pubchem.ncbi.nlm.nih.gov/compound/Sofpironium-Bromide. Accessed Sept. 2, 2025. **9.** Pariser D, Glaser D, Green L, Walker P. Sofpironium Topical Gel, 12.45%, Mechanism of Action for Primary Axillary Hyperhidrosis. Presented at: AAD Innovation Academy (Summer AAD); July 10-13, 2025; Chicago, IL. **10.** Data on File. Botanix Pharmaceuticals. P16p101. Ref-1184-SOF-v1. **11.** Data on File. Botanix Pharmaceuticals. P16c104. Ref-1322-SOF-v1. **12.** Data on File. Botanix Pharmaceuticals. 24-Nonclinical overview. Ref-1181-SOF-v1. **13.** Pariser D, et al. JAAD. 2025;93(1):82-88. **14.** Data on File. Botanix Pharmaceuticals. Ref-1182-SOF-v1 (301). **15.** Data on File. Botanix Pharmaceuticals. Ref-1183-SOF-v1 (302). **16.** Kirsch BM, et al. *JDD.* 2018;17(7):707-714. **17.** Hobart J, et al. *JDD.* 2021;20(4):410-418.