A Four-Way, Cross-Over Design, Randomized, Double-Blinded, Placebo- and Active-Controlled Study for the Evaluation of the Effect of a Supratherapeutic Dose of Sofpironium Bromide Gel, 15% Applied Topically on the QT/QTc Intervals in Adult Healthy Volunteers (BBI-4000-CL-106)

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Background

Sofpironium bromide is a retro-metabolically designed analog of glycopyrrolate (anticholinergic) in development for the topical treatment of primary axillary hyperhidrosis. Cardiac safety can be a major factor in clinical development given the potential effect of new drugs in delaying cardiac repolarization. In a study designed to mimic exposure that may occur under extreme circumstances in healthy subjects (BBI-4000-CL-109), a single 6-fold application of sofpironium bromide gel, 15% under occlusion showed a 3-fold increase in maximum sofpironium exposure compared to the intended therapeutic dose.

Objective

The prospective effect of a drug on cardiac repolarization can be measured as prolongation of the QT interval on electrocardiographic recordings. The primary objective of this thorough QT (TQT) study was to evaluate the effect of a single supratherapeutic dose (6-fold) of sofpironium bromide gel, 15% under occlusion on the Fridericia-corrected QT interval (QTcF).

Methods

This was a randomized, double-blind (with respect to the supratherapeutic dose (6-fold) of sofpironium bromide gel, 15% and placebo gel only) and active-controlled (with respect to the moxifloxacin and therapeutic dose of sofpironium bromide gel, 15%), single-dose, 4-way crossover TQT study. Sixty healthy adult male and female subjects were enrolled. On Day 1 of each period, subjects aged ≥18 to ≤55 years received one of the following investigational treatments:

- A topical ~173 mg total dose of sofpironium bromide gel, 15% (intended therapeutic dose) without occlusion to the axillae (T), or
- A topical ~1038 mg total dose of sofpironium bromide gel, 15% (supratherapeutic dose) with occlusion that was 6-fold higher than the intended therapeutic dose to the axillae, lateral side of the upper arms, ventral side of the thighs, and central abdomen (ST), or
- A topical dose of placebo gel with occlusion applied to the same sites as those used for the supratherapeutic and intended therapeutic doses (P), or
- An oral dose of moxifloxacin (400 mg) (M).

There was a washout period of at least 7 days between the dosing periods.

Figure 1: Mean Plasma Concentration of Sofpironium[1]

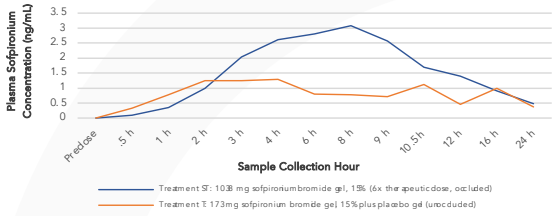

Figure 2: Placebo-Corrected Change-from-Baseline QTcF Across Time Points

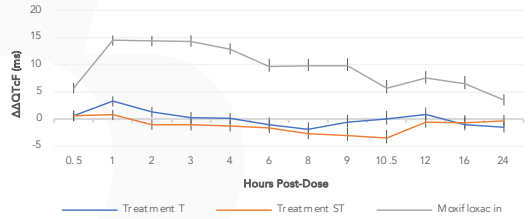

Table 1: Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population) (≥5%)

	Treatment				
ADVERSE EVENTS	T	ST	P	M	TOTAL
Number of Subjects Dosed	**59 (100%)**	**60 (100%)**	**60 (100%)**	**58 (100%)**	**60 (100%)**
Number of Subjects With TEAEs	**17 (29%)**	**43 (72%)**	**54 (90%)**	**12 (21%)**	**57 (95%)**
Number of Subjects Without TEAEs	**42 (71%)**	**17 (28%)**	**6 (10%)**	**46 (79%)**	**3 (5%)**
Application site erythema	3 (5%)	28 (47%)	41 (68%)	0 (0%)	47 (78%)
Application site pain	2 (3%)	18 (30%)	22 (37%)	0 (0%)	33 (55%)
Application site pruritis	1 (2%)	18 (30%)	17 (28%)	0 (0%)	28 (47%)
Application site exfoliation	7 (12%)	8 (13%)	2 (3%)	0 (0%)	14 (23%)
Headache	2 (3%)	3 (5%)	3 (5%)	2 (3%)	9 (15%)
Dermatitis contact	2 (3%)	0 (0%)	1 (2%)	1 (2%)	3 (5%)
Oropharyngeal pain	0 (0%)	2 (3%)	0 (0%)	1 (2%)	3 (5%)
Pruritus	0 (0%)	2 (3%)	1 (2%)	0 (0%)	3 (5%)
Upper respiratory tract infection	0 (0%)	2 (3%)	1 (2%)	0 (0%)	3 (5%)
Vision blurred	1 (2%)	2 (3%)	0 (0%)	0 (0%)	3 (5%)

Results

Administration of ~1038 mg sofpironium bromide gel, 15% (occluded) resulted in a 3.2-fold increase in C_{max} compared to the ~173 mg dose of sofpironium bromide gel, 15% (unoccluded). Mean placebo-corrected change-from-baseline QTcF (ΔΔQTcF) ranged from -3.5 ms on the supratherapeutic treatment at 10.5 hr post-dose to +3.3 ms on the therapeutic treatment at 1 hr post-dose. An effect on ΔΔQTcF exceeding 10 ms could be excluded with both sofpironium bromide gel, 15% doses, since the upper bound of the 90% CI was below 10 ms at all post-dose time points. Assay sensitivity was demonstrated by oral dosing with 400 mg of positive control, moxifloxacin.

Conclusion

The study constitutes a negative TQT study, as defined in ICH E14 clinical guidance. Systemic exposure increased more than 3-fold following supratherapeutic dosing under occlusion, but no clinically relevant changes in the QTc interval, heart rate, or cardiac conduction were noted. Therapeutic (unoccluded) and supratherapeutic (occluded, 6-fold) doses of sofpironium bromide gel, 15% appeared to be safe and generally well tolerated.

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