

# Investigating Treatment of Primary Axillary Hyperhidrosis With a Topical Retrometabolic Anticholinergic Drug

Nicholas Bodor, PhD<sup>1</sup>, Adam Friedman, MD<sup>2</sup>, Stacy Smith, MD<sup>3</sup>, James Del Rosso, MD<sup>4</sup>, Janet Dubois, MD<sup>5</sup>, Adelaide Hebert, MD<sup>6</sup>, Tory Sullivan, MD<sup>7</sup>, Zakiya Rice, MD<sup>8</sup>, Joe Gorelick, NP<sup>9</sup>, Leon Kircik, MD<sup>10</sup>, Lawrence Green, MD<sup>2</sup>, Brandon Kirsch, MD<sup>11</sup>, Deepak Chadha<sup>12</sup>, MS, MBA

<sup>1</sup>Bodor Laboratories, Miami, FL, <sup>2</sup>George Washington University School of Medicine, Washington, DC, <sup>3</sup>California Dermatology and Clinical Research Institute, Encinitas, CA, <sup>4</sup>JDR Dermatology Research/Thomas Dermatology, Las Vegas, NV, <sup>5</sup>DermResearch, Inc., Austin, TX, <sup>6</sup>Department of Dermatology, The University of Texas Health Science Center, Houston, TX, <sup>7</sup>Sullivan Dermatology, North Miami Beach, FL, <sup>8</sup>Department of Dermatology, Emory University School of Medicine, Atlanta, GA, <sup>9</sup>California Skin Institute, San Jose, CA, USA, <sup>10</sup>Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, <sup>11</sup>Kirsch Dermatology, Naples, FL, <sup>12</sup>Brickell Biotech, Inc., Boulder, CO

## Background

Anticholinergic medications are useful for the management of primary axillary hyperhidrosis (AHH). However, due to inhibition of cholinergic receptors in tissues other than the targeted sweat glands, the use of both oral and topical anticholinergics for the treatment of AHH often results in systemic side effects, such as dry mouth, blurred vision, mydriasis, and urinary hesitation. Sofpironium bromide (SB) is a novel, quaternary ammonium, anticholinergic drug that is a retrometabolically designed structural analogue of glycopyrrolate.

## Objective

A need exists to find new anticholinergics with maximal therapeutic benefits and minimal systemic side effects for the treatment of AHH. Retrometabolic drug design is intended to create drugs with an increased therapeutic index by integrating metabolism considerations into the drug design process.<sup>1</sup>

## Methods

Unlike glycopyrrolate, SB includes a readily hydrolyzable ester moiety. To obtain this metabolically sensitive site, the "inactive metabolite" approach to retrometabolic drug design was used.<sup>1</sup> A hydrolytically sensitive function was introduced in a remote site of the molecule, away from the pharmacophore.<sup>2</sup> The molecular structure was further refined based on binding to the relevant muscarinic receptors, and the most potent optical isomer was selected.<sup>3</sup> The specific enzyme responsible for hydrolytic metabolism of SB was identified.<sup>4</sup> Here we review existing pharmacokinetic and pharmacodynamic data for the retrometabolically designed investigational drug SB.

## Results

Binding studies at human muscarinic receptors (M1–M4) and guinea-pig ileum assays have found SB to have potency close to glycopyrrolate with a shorter duration of action.<sup>2</sup> The mydriatic effects of SB were compared to those of glycopyrrolate in rabbits,<sup>2</sup> where the activity of SB and glycopyrrolate lasted for approximately 48 hours and 144 hours, respectively. In vitro SB half-life in human plasma was short (3.86 hours). In a separate maximum-use pharmacokinetic (PK) study of SB in human subjects with AHH, 3-fold supratherapeutic application to the axillae, thighs, and palms had no meaningful impact on systemic exposure compared with the intended therapeutic dose.<sup>5</sup> Systemic exposure to SB and its major metabolite BBI-4010 was minimal with most samples <1 ng/mL and many results below the limit of quantitation.<sup>5</sup> To date, more than 1300 subjects have been exposed to SB across various clinical studies, and <5% subjects have been discontinued due to adverse events.

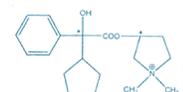
## Conclusion

SB is an anticholinergic agent synthesized according to the principles of retrometabolic drug design. Both nonclinical and clinical studies support the concept that the retrometabolic design of SB may confer certain safety and PK benefits without compromising desired anticholinergic effect.

## Sofpironium Bromide Comparison to Glycopyrrolate

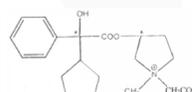
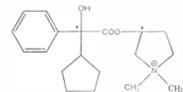
Once in circulation, sofopironium bromide rapidly hydrolyzes into its metabolite (BBI-4010), a less active anticholinergic agent, therefore reducing its potential for side effects

### Glycopyrrolate



NO  
REACTION

### Sofpironium Bromide



BBI-4010

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## References

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