NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	217347
Priority or Standard	Standard
Submit Date(s)	September 23, 2022
Received Date(s)	September 23, 2022
PDUFA Goal Date	September 23, 2023
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	September 22, 2023
Established/Proper Name	Sofpironium bromide
(Proposed) Trade Name	Sofdra
Pharmacologic Class	Anticholinergic
Code name	BBI-4000
Applicant	Botanix pharmaceuticals
Dosage form	Gel
Applicant proposed Dosing Regimen	one pump actuation per underarm administered topically once a day at bedtime
Applicant Proposed Indication(s)/Population(s)	primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	primary axillary hyperhidrosis
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	N.A.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N.A.
Recommended Dosing Regimen	N.A.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Craig Johnson, PharmD
Nonclinical Reviewer	Xinguang Cindy Li, PhD
Nonclinical Supervisor	Barbara Hill, PhD
Nonclinical Division Director	Andrew Goodwin, PhD
Office of Clinical Pharmacology Reviewer(s)	Dipak S. Pisal, MS, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD
Pharmacometrics Reviewer(s)	Da Zhang, PhD
Pharmacometrics Team Leader	Youwei Bi, PhD
Clinical Reviewer	Roselyn E. Epps, MD, FAAP, FAAD
Clinical Team Leader	David Kettl, MD, FAAP
Statistical Reviewer	Kathleen Fritsch, PhD
Cross-Disciplinary Team Leader	David Kettl, MD, FAAP
Clinical Outcome Assessment (COA) Reviewer	Sarah Stothers, RN, MSN, MPH
COA Team Leader	Selena Daniels, PharmD, PhD
Division Director (COA)	David Reasner, PhD
Division Director (OCP)	Suresh Doddapaneni, PhD
Office Director (or designated signatory authority)	Nikolay Nikolov, MD

Additional Reviewers of Application

OPQ	Drug Substance Friedrich Burnett Lawrence Perez Drug Product Caroline Strasinger Nina Ni Manufacturing David Acevedo Christine Falabella
Microbiology	Dacie Bridge Yan Zheng
OPDP	Loretta Holmes
OSI	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief
OSE/DEPI	Sally Paprah Benjamin Booth
OSE/DMEPAI	Madhuri Patel Carlos M Mena-Grillasca, Human Factors: Matthew Barlow Jason Flint Safety Evaluator: Peggy Rahbani
OSE/DPV	Vicky Chan Melissa Reyes

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

DMEPAI=Division of Medication Error Prevention and Analysis I
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Xinguang C. Li, PhD	OII/DPT-II	Sections: 5, 16.3	Select one: _X__ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Barbara Hill, PhD	OII/DPT-II	Sections: 5, 16.3	Select one: ___ Authored __X_ Approved
	Signature:			
Nonclinical Division Director	Andrew Goodwin, PhD	OII/DPT-II	Sections: 5, 16.3	Select one: ___ Authored _X__ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Dipak Pisal, MS, PhD	OCP/DIIP	Section:6, 16.4.0	Select one: __X_ Authored ___ Approved
	Signature:			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DIIP	Section:6, 16.4.0	Select one: ___ Authored __X_ Approved
	Signature:			
Pharmacometrics Reviewer	Da Zhang, PhD	OCP/DPM	Section:16.4.2,16.4.3	Select one: __X_ Authored ___ Approved
	Signature:			
Pharmacometrics Team Leader	Youwei Bi, PhD	OCP/DPM	Section: 16.4.2,16.4.3	Select one: ___ Authored _X__ Approved
	Signature:			
Clinical Pharmacology Division Director	Suresh Doddapaneni, PhD	OCP/DIIP	Section: 6, 19.4	Select one: ___ Authored __X_ Approved
	Signature:			
Clinical Reviewer	Roselyn E. Epps, FAAP, FAAD	Office of Immunology and Inflammation (OII)/DDD	Sections: 1.1, 1.3, 1.4, 2, 3, 4.1, 7, 8.2, 9, 10, 12, 13, 16.1, 16.2	Select one: __X_ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	David Kettl, MD	OII/DDD	Sections: 1.1, 1.3, 1.4, 2, 3, 4.1, 7, 8.2, 9, 10, 12, 13	Select one: ___ Authored __X_ Approved
	Signature:			
Division Director (Clinical)	Shari L Targum, MD, MPH	OII/DDD	Sections: 14	Select one: __X_ Authored __X_ Approved
	Signature:			
Statistical Reviewer	Kathleen Fritsch, PhD	OB/DBIII	Sections: 1.2, 8.1, 8.3	Select one: _X__ Authored _X__ Approved
	Signature:			
Division of Clinical Outcome Assessment Reviewer	Sarah Stothers, RN, MSN, MPH	ODES/DCOA	Sections: 8.1.4, 16.5	Select one: _X__ Authored _X__ Approved
	Signature:			
Division of Clinical Outcome Assessment Team Leader	Selena Daniels, PharmD, PhD	ODES/DCOA	Sections: 8.1.4, 16.5	Select one: ___ Authored _X_ Approved
	Signature:			
DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Division of Clinical Outcome Assessment Division Director	David Reasner, PhD	ODES/DCOA	Sections: 8.1.4, 16.5	Select one: ___ Authored __X Approved

	Signature:

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GGT	gamma glutamyl transferase
GRMP	good review management practice
HDSS	Hyperhidrosis Disease Severity Scale
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PAH	primary axillary hyperhidrosis
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SB	sofpironium bromide
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Sofpironium bromide gel is a new molecular entity and small molecule, quaternary ammonium analogue of anticholinergic drug glycopyrrolate. The Applicant proposes the product for primary axillary hyperhidrosis in adult and pediatric patients 9 years and older. The mechanism of action to reduce sweat production is by selective, competitive inhibitor of muscarinic receptor type 3 (M3), which is the predominate receptor in the axillary eccrine glands which provide the watery secretions of hyperhidrosis.

Sofpironium bromide gel is an (b) (4) formulation containing the drug substance in a gel base. Sofpironium bromide gel is clear to slightly translucent, and colorless to pale yellow in color and packaged in a metered pump container. The Applicant proposes to apply sofpironium bromide gel by one pump actuation per underarm daily at bedtime. The product should be applied by using one actuation onto the pump cap, which is used to apply the gel product. The proposed proprietary name is Sofdra.

The product was known as BBI-4000 early in development and sofpironium bromide, and the names are used interchangeably in this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant provided substantial evidence of effectiveness from two adequate and well-controlled trials (Studies BBI-4000-CL-301 and BBI-4000-CL-302) of sofpironium bromide gel, 15% versus vehicle in the treatment of primary axillary hyperhidrosis. Each trial was multicenter, randomized, double-blind, and vehicle controlled and enrolled approximately 350 subjects 9 years of age and older. Subjects applied treatment (sofpironium bromide gel 15% or vehicle) once daily at bedtime to each axilla for 42 days. At screening and baseline, subjects were to have

- Hyperhidrosis Disease Severity Measure-Axillary-7-item (HDSM-Ax-7) scale score of 3 to 4
- A minimum of 50 mg of sweat production at rest (gravimetric test) in each axilla with a two-axilla combined total of at least 150 mg of sweat production in 5 minutes at room temperature
- Symptoms of axillary hyperhidrosis for ≥6 months' duration

The co-primary efficacy endpoints in Studies BBI-4000-CL-301 and BBI-4000-CL-302 were the proportion of subjects with ≥2 point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT) and the change from baseline to EOT in gravimetric sweat production

(GSP). Both endpoints were statistically significant in each study based on the protocol-specified primary analyses.

Because different versions of the HDSM-Ax were used to generate the HDSM-Ax-7 scale score for children ≥9 to <12 years of age and adolescents and adults ≥12 years of age, it would not be appropriate to combine the results from both instruments. Across the two studies, only 5 subjects ≥9 to <12 years of age were enrolled and evaluated using the HDSM-Ax-7 scale – Child Version. Therefore, the recommended presentation of results for the HDSM-Ax-7 response endpoint is to use the analysis for subjects ≥12 years of age (HDSM-Ax-7 scale – Adult Version). For the change in GSP endpoint, the protocol specified that the analysis was conducted on the ranked values rather than the measured values if the test for non-normality was significant. While using a ranked analysis minimizes the impact of the skewness of the distribution on the analysis and provides a p-value for assessing statistical significance, estimates based on the difference in ranks are not clinically meaningful. Therefore, the results for the change in GSP endpoint are also presented using medians and the quartiles (25th and 75th percentiles). The co-primary efficacy results are presented in Table 1.

Table 1 – Co-primary Efficacy Results in Studies 301 and 302 (ITT; multiple imputation)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
≥2 point improvement in HDSM-Ax-7 scale score **(≥12** years)	N=172	N=177	N=178	N=169
Estimated percentage	50.4	32.1	63.3	47.1
Treatment difference (95% CI)	18.3 (8.0, 28.7)		16.2 (5.4, 26.9)	
p-value	0.0005		0.0040	
Change from Baseline in GSP	N=173	N=177	N=180	N=171
Difference in Ranks [LS Means (SE)]	-14.9 (6.8)	14.8 (6.7)	-9.9 (7.1)	11.8 (7.5)
p-value	0.0019		0.0296	
Median Change from Baseline Values [mg]	-127.8	-100.3	-142.6	-134.2
25th percentile, 75th percentile	-200.5, -52.4	-227.5, -28.5	-260.1, -75.0	-230.0, -59.5

CI= confidence interval; LS=Least squares; SE= standard error
Source: Clinical Study Report 301 (page 62, 173) and Clinical Study Report 302 (page 64, 180); findings reproduced or conducted by the statistical reviewer using adhdsmi.xpt and adgspmi.xpt.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Sofdra (Sofpironium bromide) gel is a new molecular entity and small molecule, quaternary ammonium analogue of anticholinergic drug glycopyrrolate. The Applicant proposes the product for the indication primary axillary hyperhidrosis in adult and pediatric patients 9 years and older. The drug intends to decrease excessive perspiration localized to the underarm areas. The study drug is contained in a metered pump bottle, with an applicator cap over the dispenser and a covering cap. The recommendation of the team is a Complete Response.

Primary axillary hyperhidrosis (PAH) is localized excessive perspiration beyond what is needed for body temperature control. Increased moisture in the body folds can result in maceration, dermatitis, and infection. Embarrassment has been reported. Available treatment options include OTC antiperspirants, topical aluminum chloride products, cool clothing selection, ambient temperature adjustment. FDA-Approved prescription products are topical glycopyrronium cloths used as a wipe and onabotulinumtoxinA injections to the axillary areas. Multiple FDA-cleared devices for hyperhidrosis utilize iontophoresis, thermal energy, ultrasound, and laser techniques. For unresponsive symptoms, surgical and sympathectomy treatments are used. This drug would provide an additional, locally-acting, reversible treatment.

Clinical trials demonstrated effectiveness. The co-primary efficacy endpoints in clinical trials BBI-4000-CL-301 and BBI-4000-CL-302 in adults were the proportion of subjects with ≥2 point improvement in HDSM-Ax-7 from baseline to EOT and the change from baseline in GSP from baseline to EOT. Both endpoints were statistically significant in each study based on the protocol-specified primary analysis. The Applicant used two clinical outcomes assessment (COA) instruments during the trials, for ages 9 to 11 years and for 12 years and older.

Though variable, the absorption of sofpironium bromide gel was generally low. An additional option which is topical and noninvasive would be of benefit.

The main safety considerations are anticholinergic side effects, including dilated pupils, blurry vision, dry eye, dry mouth, constipation, and urinary hesitation. The most common local skin reactions >1% and more frequent in the study group vs. vehicle included application site pain, redness, dermatitis and itching. Overall, adverse events were reversible and mild to moderate in severity. ECG changes and cardiac adverse events were not considered clinically significant.

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient or others, or compromised efficacy. Specifically, the review of the human factors study noted that there are risks associated with potential underdose,

overdose and inadvertent exposure to others, with symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. The Agency review identified areas of vulnerability that may lead to medication errors. The review team recommends that Botanix SB, Inc. review the results of the HF validation study along with the root cause analysis and subjective feedback, consider additional design modifications, implement our recommendations, and conduct another HF validation study to demonstrate that the product user interface supports safe and effective use.

Despite the overall conclusion that effectiveness was adequately demonstrated, and that safety events in the clinical trial were not substantial, the deficiencies in the human factors information does not support an approval of this application due to the risks of medication errors and adverse reactions due to inappropriate drug administration. This issue was communicated to the applicant in a discipline review letter dated September 8, 2023.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hyperhidrosis, excessive perspiration beyond what is necessary for thermoregulation, can be generalized or localized (focal). Primary axillary hyperhidrosis (PAH) is a focal type thought to be secondary to excessive activity of the eccrine glands in the axillae and stimulated by acetylcholine nerves with no underlying cause identified. Onset is often under age 25 years and excessive moisture can cause intertriginous maceration or infection, as well as discomfort and embarrassment.	PAH moisture in intertriginous areas can lead to maceration, dermatitis, intertrigo and infection. Treatment of localized, axillary hyperhidrosis would allow for continued thermoregulation without excessive sweat production and the secondary complications. Additionally, PAH treatment would reduce embarrassment.
Current Treatment Options	• The first-line treatments are OTC antiperspirants, topical aluminum chloride products, and attention to cool clothing selection, ambient temperature and other exacerbating factors. FDA-Approved prescription products are topical glycopyrronium cloths used as a wipe and onabotulinumtoxinA injections to the axillary areas. Multiple FDA-cleared devices for hyperhidrosis utilize iotophoresis, thermal energy, ultrasound, and laser techniques to reduce or eliminate axillary sweating. For unresponsive disease, surgical sympathectomy or excision of sweat glands have been a last recourse for PAH unresponsive to treatments.	There are multiple treatment options and modalities available for PAH; however, there is one FDA-approved topical drug treatment for PAH. The effectiveness of the therapies varies and the response can be insufficient.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In two identical phase 3 clinical trials, sofpironium gel showed efficacy vs. vehicle, and met the primary and secondary endpoints. PK assessed absorption as low and variable. QTc testing did not show relevant anticholinergic cardiac adverse events. • Sofpironium bromide is a gel used once a day, which can be applied as an outpatient. The mechanism of action is anticholinergic, acting on the axillary eccrine glands directly through local absorption without invasive or parenteral methods. The predominant side effects reported during clinical trials related to study drug were dry mouth, mydriasis, and blurred vision and local skin reactions. The adverse events reported were reversible and rarely severe.	An additional topical home treatment option would be of benefit, which is noninvasive, reversible, and applied to the skin by the patient rather than injected or resulting in permanent skin alterations after a procedure.
Risk and Risk Management	• The Sofpironium gel is a combination drug product composed of the gel within a metered pump container. The cap of the pump container is intended as an applicator. Each pump actuation delivers approximately 0.67 mL of the gel formulation. • The instructions for use (IFU) were detailed with densely spaced print on a document folded accordion-style. Studying of human factors found that adult patients and caregivers demonstrated difficulties with the basic tasks of depositing the gel on the applicator (for underarm 1 & 2) and applying to the underarm (for underarm 1 & 2), as well as not handwashing after use. The difficulties demonstrated increase the risk of overuse, and transfer of drug product to other body areas and other persons.	Use issues result in associated potential harm of overdose, underdose, and accidental exposure to others. Recommended changes: a full IFU revision (e.g., revising the format, layout, and information density and salience); directly labeling the applicator with its intended use/purpose (e.g., how many pumps to apply); redesign the user interface. Revalidate changes for all user groups prior to approval.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.2.11
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		See DCOA review for full discussion on qualitative studies
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
X	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	X	Patient-focused drug development or other stakeholder meeting summary reports		Not Applicable
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Hyperhidrosis is excessive perspiration beyond what is necessary for thermoregulation. Hyperhidrosis can be generalized or localized, also known as focal hyperhidrosis (FH). Primary FH presents on the axillae, palms, and/or soles frequently, and meets certain criteria: Focal, visible, excessive sweating of at least six months duration without apparent cause plus at least two of the following characteristics: bilateral and relatively symmetric; impairs daily activities; at least one episode per week; onset before age 25; family history of idiopathic hyperhidrosis; focal sweating stops during sleep.

Axillary hyperhidrosis is a focal type thought to be secondary to excessive activity of the eccrine glands. The eccrine glands concentrated in the axillae are stimulated by acetylcholine nerves resulting in watery secretions typical of hyperhidrosis. While a cause for some types of hyperhidrosis can be identified such as thyroid disease, hypoglycemia, and medications, the underlying etiology for primary axillary hyperhidrosis (PAH) is not known. PAH can be influenced but not caused by factors including anxiety or stress, ambient temperature, and clothing choice. During axillary hyperhidrosis episodes clothing becomes soaked, and excessive moisture can lead to intertriginous dermatitis, maceration, and occasional infection. Some affected by PAH report discomfort and embarrassment. (Hornberger et al. 2004)

While FDA-approved and cleared therapies are available for PAH, none works for all patients and additional treatment options are needed.

2.2. Analysis of Current Treatment Options

Treatments for PAH begin with environmental and over-the-counter (OTC) approaches including clothing selection to minimize moisture, ambient temperature, antiperspirant use including aluminum chloride products. The two prescription drugs approved for the PAH indication are Qbrexza (glycopyrronium tosylate) cloth wipes for ages 9 years and older and Botox (onabotulinumtoxinA) injections for ages 12 years and older. Multiple devices are FDA-cleared for the hyperhidrosis indication and function by iontophoresis and microwave thermolysis. Surgical interventions including excision and endoscopic thoracic sympathectomy are reserved for the most resistance and disabling cases. Off-label use of oral medications is known, including glycopyrrolate and oxybutynin.

Table 2: Summary of Currently Available Treatments for Primary Axillary Hyperhidrosis

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Drug Treatments						
Qbrexza 2.4% cloths (glycopyr-ronium tosylate)	Topical treatment of primary axillary hyperhidro-sis in adults and pediatric patients 9 years of age and older	2018	Apply once daily to both axillae using a single cloth	From labeling co-primary endpoints: proportion of subjects ≥ 4-point improvement from baseline at Week 4: wkly mean ASDD item #2 score; mean absolute change in gravimetrically measured sweat production.	W&P from labeling: -New/ worsening urinary retention. Caution if Hx documented urinary retention -Heat illness may occur in high ambient temps. Avoid if ↓ sweating generally in hot/very warm envtl temps -Transient blurred vision. Avoid operating motor vehicle/ machinery until Sx resolve	Contraindicated from labeling: glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjogren's syndrome
Botox ® (onabotulin-umtoxinA) for injection	Treatment of severe axillary hyperhidros is that is inadequate-ly managed by topical agents in adult patients	2004; Efficacy supple ment	In office injections: 50 U each axilla	From labeling: success ≥ 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks.	Adverse Rxn: injection site pain; hemorrhage non-axillary sweating, pharyngitis, flu syndrome	W&P: spread of toxin effects, swallowing & breathing difficulties; pts with neuromuscul ar diseases, compromised respiratory Fxn.
Other Treatments – Cleared Devices						
Iontophoresis (multiple	Treatment of axillary	1990 – 2020	Topical. Use 20-30	510(k) devices	discomfort, dryness,	Caution/

cleared devices: RH-900; Drionic; Dermadry)	hyperhidrosis		minutes several times a week for effect, then maintenance q 1-4 weeks		paresthesia, erythema, transient vesiculation of the affected area	avoid use: Pregnancy, substantial implants, cardiac conditions, epilepsy, implantable electronic devices, including pacemakers.
miraDry® (DTS-G2 System)	PAH age 18 years and older	2011	Topical, microwave thermolysis device. In-office procedure. Tx x 1-3	Prospective, blinded, controlled. Randomized 2:1 (Tx:sham) Hyperhidrosis Disease Severity Scale (HDSS) 1 or 2 at 30 days. P < 0.001	Aes: Altered sensation swelling, redness, and tenderness lasting for several days. Numbness and tingling	

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sofpironium bromide is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

March 5, 2014: Type B Pre-IND Meeting with Brickell Biotech, Inc. Detailed recommendations were provided by multiple disciplines for the BBI-4000 gel development program: Chemistry, Manufacturing and Controls (CMC) Pharmacology/Toxicology; Clinical.

December 24, 2014: Opened IND 121256 with Phase 2 trial evaluating 3 concentrations of topical BBI-4000 gel in subjects with primary axillary hyperhidrosis. Study considered safe to proceed.

June 14, 2017: Advice Letter: Recommendations regarding phase 2 trial 203 included:

- Co-primary endpoints that consist of
    - an objective assessment (such as change in gravimetrically measured sweat production) and
    - a responder's definition based on a certain threshold level (e.g., 2-point change) on a validated HDSM-Ax scale for Phase 3 trials to ensure that the primary endpoint represents a clinically meaningful improvement.
- Phase 3 trials should be powered for the recommended co-primary endpoints with power of at least 80% at 2-sided α=0.05.

February 7, 2018: Type B, End of Phase 2 Meeting. Recommendations of note include:

- Division of Medication Error Prevention and Analysis I (DMEPAI) stated that a comprehensive risk analysis or plan for a Human Factors (HF) validation study had not been submitted. The Agency recommended conducting a comprehensive use-related risk analysis to include a comprehensive and systematic evaluation of all the steps involved in using your metered dose pump (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. With the garnered information and data, the Sponsor should determine whether or not a human factors (HF) validation study would be needed. If an HF validation study were not needed, the Sponsor needed to submit the risk analysis, comparative analyses, and justification for not conducting the HF validation study to the Agency for review under the IND.

February 7, 2022: Type B Pre-NDA Meeting

Noted: CMC information described in the meeting package was not sufficient to support filing

and review; the requirements were conveyed. Comments were provided and discussed with the Sponsor regarding the psychometric analysis plan and statistical analysis plans including scores from the adult version (for patients aged ≥12 years) and child version (for patients ≥9 to < 12 years of age) of the HDSM-Ax-7.

APPEARS THIS WAY ON ORIGINAL

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Four sites total were inspected as a routine PDUFA inspection for trial 301 and 302. Two sites were selected for each phase 3 trial. The inspections occurred during the BLA review.

- Dr. Zoila Alen (Site 1016). This was the first FDA inspection of this investigator. This site was selected because no AEs were reported.
- Dr. Tory P. Sullivan (Site 1004). The previous OSI inspection was without significant findings.
- Dr. Maryellen Fitzgerald (Site 2052). This was the first FDA inspection of this investigator.
- Dr. Scott A. Smith (Site 2051). This was the first FDA inspection of this investigator.

Of the four sites selected, inspections identified no discrepancies at one 301 site (Dr. Alen); the inspection found no unreported AEs or SAEs. The Office of Scientific Investigations (OSI) identified objectionable conditions at the other sites (one 301 site and two 302 sites). The sites' written responses were received noting implementation of corrective actions to prevent the recurrence of the inspection findings; no further action was required.

The conclusion of OSI was that the inspection conditions at the sites "having some findings, which are unlikely to have significant impact on study efficacy results or safety assessment, overall, the two studies appear to have been conducted adequately, and the data generated by the inspected clinical investigators and submitted by the Applicant appear acceptable in support of the proposed indication."

4.2. Product Quality

Based on the OPQ evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate chemistry, manufacturing, and controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. However, the comments to the proposed labeling and labels have not been communicated to the applicant as labeling was precluded this review cycle.

As such, from the OPQ perspective, this NDA is not ready for approval in its current form until the labeling deficiencies and recommendations are appropriately addressed as per 21 CFR 314.125(b)(6).

4.3. Clinical Microbiology

Not applicable to this application.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this application.

APPEARS THIS WAY ON ORIGINAL

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant submitted a 505(b)(1) application for their proposed product, sofpironium bromide topical gel, 15% (12.45% free base) to treat primary axillary hyperhidrosis in adults and children aged 9 years and older. The active ingredient of the product, sofpironium bromide, is a new molecular entity and is designed as a novel ester analogue of glycopyrrolate which is an acetylcholine antagonist.

The nonclinical studies submitted under the NDA include pharmacology, pharmacokinetics and toxicology studies with sofpironium bromide. The pivotal toxicology studies consist of chronic repeat dose toxicology studies, a battery of genetic toxicity studies, two carcinogenicity studies, reproductive and development toxicity studies, and special toxicity studies including skin irritation and sensitization study, ocular irritation study, and phototoxicity study.

Sofpironium bromide (code name; BBI-4000) has been evaluated in repeat-dose subcutaneous toxicity studies in rats for up to 26 weeks, and in repeat-dose dermal toxicity studies in Göttingen minipigs for up to 39 weeks. The major treatment-related effects observed in repeat-dose studies were findings at the test article administration sites. Pharmacologic anticholinergic effects were observed in rats with subchronic or chronic subcutaneous administration at doses of ≥1.5 mg/kg/day.

Repeat dose dermal bridging studies were also conducted in minipigs to assess potential differences between the original sofpironium bromide gel formulation containing (b) (4) and the reformulated to be marketed sofpironium bromide gel formulation containing Isopropyl Myristate (IPM). The 28-day repeat dose minipig study showed that the systemic exposure following administration of sofpironium bromide gel was approximately 2-fold higher for the IPM formulation than for the (b) (4) formulation. However, no toxicologically relevant differences were identified between the two formulations.

Sofpironium bromide was not mutagenic or clastogenic in the bacterial reverse mutation assay, in vitro mammalian chromosome aberration assay, and rat in vivo micronucleus assay.

In the 2-year dermal mouse carcinogenicity study, there was no evidence of neoplastic effect associated with unoccluded 23 hr/day sofpironium bromide IPM gel administration to CD-1 mice. Dose levels of sofpironium bromide gel were 5%, 10% or 20% gel, respectively. Administration of sofpironium bromide gel caused dermal irritation associated with slight epidermal hyperplasia in all treatment groups.

In the 2-year subcutaneous rat carcinogenicity study, there was no evidence of neoplastic effect associated with daily subcutaneous administration of sofpironium bromide for 104 weeks to SD

rats [males (0, 0.3, 0.75, 1.5 mg/kg/day) and females (0, 0.5, 1.5, 5.0 mg/kg/day)]. Sofpironium bromide administration caused injection site inflammation/degenerative changes associated with irritation.

The effect of sofpironium bromide on reproductive and development toxicity, including fertility, embryofetal development, and prenatal and postnatal development was investigated in rats or rabbits following subcutaneous (sc) administration. The sofpironium bromide no observed adverse effect level (NOAEL) for male and female fertility or early embryonic development was 10 mg/kg/day in rats following sc administration. The maternal and fetal survival, growth and development NOAEL was 10 mg/kg/day in embryo-fetal development studies in rats following sc administration. In rabbits, the NOAEL for embryo-fetal development toxicity was 2 mg/kg/day sc sofpironium bromide and the NOAEL for fetal malformation was 10 mg/kg/day. The NOAEL for the pre– and postnatal survival, growth, and maturation of the F1 and F2 offspring, and neurobehavioral development and reproductive performance of the F1 offspring was established as 6 mg/kg/day after subcutaneous administration in rats.

Subcutaneous sofpironium bromide administration to juvenile rat pups from postnatal day (PND) 7 through PND 98 did not adversely affect any developmental parameters, sexual maturation or neurobehavioral endpoints measured. A NOAEL of 5 mg/kg/day was established in this study.

Special toxicity studies conducted with sofpironium bromide gel include skin irritation and sensitization study, ocular irritation study, and phototoxicity study. Sofpironium bromide gel (20%) elicited ocular irritation based on the results of the Bovine Corneal Opacity and Permeability assay. Sofpironium bromide is a skin irritant but not a sensitizer. Sofpironium bromide was not phototoxic based on no absorption in the UVB/UVA/Vis spectrum (290-700 nm).

The major metabolite of sofpironium bromide is BBI-4010. It is the only metabolite that exceeded 10% of total drug exposure in plasma and/or urine of rats, minipigs and humans. BBI-4010 exhibited significantly greater exposure noted in the rat toxicity studies compared to that in humans. The potential toxicity of BBI-4010 was evaluated within studies conducted for sofpironium bromide. Systemic exposure to BBI-4010 was also measured along with sofpironium bromide (BBI-4000) in the pivitol toxicology studies.

There are no novel excipients in the proposed product, sofpironium bromide IPM gel.

No issues have been identified with impurities. During drug product development, two potential diastereomeric impurities of sofpironium bromide, (b) (4) and three potential drug product degradants, (b) (4) (b) (4) were evaluated for potential genotoxicity in vitro, and for general toxicity in 4-week toxicity studies in rodents. None of the

impurities or degradants demonstrated mutagenic potential or added any changes to the toxicity or toxicokinetic profiles of sofpironium bromide in the in vivo toxicity studies.

In summary, the nonclinical assessment did not identify any safety concerns for the proposed product that are considered to be an approval issue. For the NOAEL determined in the pivitol toxicology studies with sofpironium bromide, there are adequate safety margins when systemic exposure of sofpironium bromide is compared between animals and humans topically treated with sofpironium bromide gel, 15%. The NOAEL of sofpironium bromide gel in animal dermal toxicology studies are generally 20% which is higher when compared to the 15% concentration in clinical studies. In addition, some findings noted in the subcutaneous toxicity studies at local injection site are not clinically relevant since the clinical use will be topical administration. Refer to Section 19.3.1 for multiples of exposure based on AUC comparisons between the NOAEL from nonclinical studies and the maximum recommended human dose (MRHD) from clinical studies.

This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Sofpironium bromide is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. It indirectly reduces the rate of sweating by preventing the stimulation of these receptors. A series of in vitro, ex vivo and in vivo pharmacological studies were conducted to characterize the pharmacology profile of sofpironium bromide and its primary metabolite, BBI-4010.

Primary Pharmacology

In primary pharmacology studies in vitro, sofpironium bromide exhibited high binding affinity for all muscarinic receptors with a high selectivity for M3, the predominant muscarinic receptor in sweat glands. The binding affinity of sofpironium bromide was less than that measured for glycopyrrolate for all other muscarinic receptors. There was no difference in binding activity or subtype selectivity between sofpironium bromide and the sofpironium (b) (4)
The major metabolite, BBI-4010, showed approximately one order of magnitude less binding affinity for M3 and M2 than the sofpironium bromide parent drug.

Ex vivo, the inhibitory activity of sofpironium bromide was less potent than glycopyrrolate in the isolated guinea pig ileum model of C-Ch-stimulated contraction. In the same model, BBI–4010 exhibited 1200-fold lower anticholinergic activity than the parent compound.

In vivo topical ocular dosing with 0.1% and 1% sofpironium bromide induced dose-dependent mydriasis in rabbits. The effect was less than that observed with 0.2% glycopyrrolate. Mydriasis has also been observed following sc administration of sofpironium bromide in repeat dose toxicity studies in rats and rabbits but has not been observed in minipigs following topical administration of sofpironium bromide gel.

An in vivo pharmacology study was conducted to evaluate the ability of sofpironium bromide to inhibit muscarinic receptor-induced perspiration in SD rats. In comparison with a concurrent ethanol control group, a single topical application of sofpironium bromide gel at a 20% concentration statistically significantly inhibited perspiration induced by subcutaneous injection of the muscarinic receptor agonist pilocarpine. This study demonstrated that topically applied sofpironium bromide effectively reduced sympathetic nerve over-activity at the site of application.

Secondary Pharmacology

In vitro screening assays showed that sofpironium bromide did not exert any significant activity against the majority of evaluated enzymes and receptors with the exception of the intended inhibition of muscarinic receptors.

Following topical administration of 15% sofpironium bromide gel, the inhibition of rat L-type calcium channels (benzothiazepine and phenylalkylamine) occurred at IC_{50} values which were 307-fold and 80-fold higher, respectively, than the human plasma sofpironium level (11.2 ng/mL).

BBI-4010 did not exhibit any significant inhibition or stimulation in any enzyme or radioligand assay in pharmacologic screening assays.

Safety pharmacology

In vitro, sofpironium bromide was shown to inhibit the Ikr current in a hERG assay with an IC_{50} value of >300 µM, an approximate 350-fold higher exposure than that was measured clinically.

In a 28-day repeat-dose toxicology study, sofpironium bromide did not show any effects on autonomic functions, behavior, reflex or appearance in SD rats following 28 days of repeated subcutaneous injections at 1, 5, or 10 mg/kg/day.

Single iv administration of sofpironium bromide to telemetered female beagle dogs of up to 1.0 mg/kg were associated with pharmacologically mediated tachycardia, an expected anticholinergic effect. Compensatory increases in diastolic pressure were noted at doses ≥0.01 mg/kg. There were no sofpironium bromide related effects on electrocardiographic (ECG) waveforms or intervals (RR, PR, QRS, QT, QTc). There were no adverse effects on respiratory parameters (rate, tidal volume or minute volume) or body temperature at any dose level. The cardiopulmonary no-observable-effect-level (NOEL) for iv sofpironium bromide was 0.001 mg/kg.

Additional ECG evaluations following topical application of sofpironium bromide (b) (4) gel, 20% were conducted in a 28-day toxicity study in Sinclair miniature swine and in a 39-week chronic study in Göttingen minipigs. There were no sofpironium bromide related effects on ECG parameters (heart rate, waveform, or RR, PR, QRS, QT, QTc intervals) in either study.

An in vivo safety pharmacology study was conducted in a murine colonic propulsion model to investigate the potential for sofpironium bromide to inhibit colonic propulsion due to pharmacologically mediated anticholinergic effects. Based on time to expulsion of a glass bead placed into the colon, mice exhibited a dose-dependent inhibition of colonic propulsion following a subcutaneous injection of 4 or 40 mg/kg sofpironium bromide. The observed effect was consistent with the expected anticholinergic activity of sofpironium bromide.

5.4. ADME/PK

Comparative systemic exposure to sofpironium and its primary metabolite, BBI-4010, following repeated once daily, dermal or sc administration of sofpironium bromide to mice, rats, minipigs and humans is provided in the following table (adapted from the NDA submission).

Table 3: Comparative Pharmacokinetic Data and Systemic Exposure to Sofpironium and BBI-4010 Following Repeat Dose Subcutaneous or Dermal Administration of Sofpironium Bromide to Mice, Rats, Minipigs and Humans

Species, Strain	Sofpironium Bromide Dose (mg/kg/day)	Route, Duration	Sofpironium Dose Form	Sofpironium		BBI-4010		Study No.
				C_{max} [1] (ng/mL)	AUC [1] (ng•hr/mL)	C_{max} [1] (ng/mL)	AUC [1] (ng•hr/mL)	
Mouse, CD1	84 (5%)	Dermal [2] 2 Weeks	IPM Gel	78.4 (7.0)	343 [3] (2.9)	8.3 (1.6)	NC (ND)	XW71GJ
	171 (10%)			179 (16.0)	859 [3] (7.2)	17.1 (3.2)	219.5 [3] (2.7)	
	354 (20%) [4]			135 (12.1)	787 [3] (6.6)	25.2 (4.7)	373 [3] (4.5)	
Mouse, CD1	83 (5%)	Dermal [2] 13 Weeks	(b) (4) Gel	210 (18.8)	1436 [5] (12.1)	18.4 (3.5)	250 [5] (3.0)	NJD0017
	168 (10%)			13.8 (1.2)	244 [5] (2.1)	15.3 (2.9)	248 [5] (3.0)	
	353 (20%)			134 (12.0)	551 [5] (4.6)	51.7 (9.7)	800 [5] (9.7)	
Rat, SD	0.5 [4]	sc 26 Weeks	Saline Solution	81.9 (7.3)	97.5 [5] (0.8)	9.6 (1.8)	17.4 [5] (0.2)	NJD0026
	1.5			258 (23.1)	371 [5] (3.1)	42.7 (8.0)	105 [5] (1.3)	
	5			531 (47.5)	1415 [5] (11.9)	87.3 (16.4)	655 [5] (7.9)	
Minipig, Göttingen	76 (20%) [4]	Dermal [2] 28 Days	(b) (4) Gel	14.5 (1.3)	71.5 [5] (0.6)	3.58 (5.9)	39.5 [5] (0.5)	NY88DH
			IPM Gel	51.0 (4.6)	200 [5] (1.7)	7.03 (0.19)	67.9 [5] (0.8)	
Minipig, Göttingen	16 (5%)	Dermal [6] 39 Weeks	(b) (4) Gel	17.0 (1.5)	76.9 [5] (0.6)	NC	ND	NJD0025
	32 (10%)			35.1 (3.1)	76.3 [5] (0.6)	NC	ND	
	67 (20%) [4]			53.9 (4.8)	246 [5] (2.1)	NC	ND	
Human	~3	Dermal [7] 14 Days	IPM Gel	11.2	119 [5]	5.32 [5]	82.8 [5]	BBI-4000-CL-103

NOTE: Numbers in parentheses represent ratios of exposure in animals to those in humans (Study BBI-4000-CL-103)

AUC=area under the plasma concentration-time curve; C_{max}=maximum concentration; (b) (4) IPM=isopropyl myristate; NC=not calculated due to insufficient plasma concentrations above the limit of quantitation; ND=not determined; sc=subcutaneous

1 Values for Cmax and AUC are combined gender (male and female)
2 Topical gel applied unoccluded for 23 hr per day and then wiped off
3 $AUC_{0\text{-}23}$ area under the plasma concentration time curve from time 0 to 23 hr postdose
4 No adverse effect level (NOAEL) dose
5 $AUC_{0\text{-}24}$ area under the plasma concentration time curve from time 0 to 24 hr postdose
6 Topical gel applied semi-occluded for 6 hr per day and then wiped off
7 Topical IPM gel (15% formulation) administered once daily to healthy subjects (n=10) for 14 days [2 pump actuations, i.e. 1 per axilla (0.67 mL/actuation) for a total dose of ~172 mg sofpironium bromide per day] ; ~3 mg/kg/day based on human body weight of 60 kg.

The major in vivo metabolites of ^{14}C-sofpironium observed in rats and minipigs are summarized in the following table (adapted from the NDA submission).

Table 4: Composition of ^{14}C-Sofpironium Metabolites in Plasma, Urine, Feces and Bile Expressed as Percent in Sample in Rats and Minipigs

Compound	Percent (%) in Sample										
	Plasma						Urine		Feces		Bile
	Rat			Minipig			Rat	Minipig	Rat	Minipig	Rat
	0.25 hr	1 hr	2 hr	0.25 hr	1 hr	2 hr	0-24 hr	0-48 hr	0-24 hr	0-72 hr	0-8 hr
Sofpironium	71.7	53.7	41.1	76.0	29.8	10.4	23.2 (11.8) [3]	4.1 (2.0) [3]	11.7 (4.3) [3]	ND	1.4 (0.4) [3]
BBI-4010 [1]	9.1	9.8	11.3	2.9	5.1	4.9	12.8 (6.6) [3]	10.6 (5.2) [3]	4.8 (1.8) [3]	2.2 (0.9) [3]	ND
(b) (4)	ND	4.1	9.5	ND	ND	ND	ND	ND	ND	ND	ND
Other peaks [2]	ND	2.7	4.1	ND	5.5	8.3	7.1 (3.6) [3]	7.6 (3.7) [3]	4.4 (1.6) [3]	11.3 (4.7) [3]	8.4 (2.7) [3]

hr=hour; (b) (4) h=hour; ND=not determined

1 BBI-4010 values are the sum of two diastereomeric peaks
2 Metabolite peaks showing the highest ratio other than sofpironium, BBI-4010, and (b) (4) are displayed; other peaks of <10% are not shown
3 Values in parentheses represent % of dose

Excretion of radioactive material following single dose administration of ^{14}C-sofpironium bromide to rats and minipigs are summarized in the following table (adapted from the NDA submission).

Table 5: **Excretion of radioactive material after Single Doses of ^{14}C-Sofpironium Bromide to Rats and Minipigs**

Species	Dose (mg/kg)	Route	Excretion as a Percentage of Administered Dose (0-168 hr)			
			Urine [1]	Feces	Expired Air	Total
Rat [2]	40	Dermal [3]	0.7±0.7	0.6±0.6	0.0±0.0	1.3±1.3 [4]
Rat	0.5	Subcutaneous	54±2.0	45.0 ± 1.9	0.1 ± 0.0	99.1 ± 0.2 [5]
Minipig [6]	0.25	Subcutaneous	52.8 ± 4.9	43.3 ± 4.8	NA	96.1 ± 0.1

hr=hour; NA=not applicable; Each value is the arithmetic mean ± standard deviation (n = 3)

1 Urine + cage wash
2 Rat Study AE-7665-G
3 Application time = 24 hr
4 After dermal administration, 90.2±2.4% of the dose was recovered in unabsorbed formulation, and 5.2 % of the dose was in the skin at the application site, for a total recovery of 96.7±0.8%
5 After subcutaneous administration to the rat, 0.6% of the dose was found in the carcass at 164 hours postdose. Total recovery was 99.7 ± 0.3% of the dose.
6 Minipig Study AE-7666-G

Type of Study	Major Findings
Absorption	
Single Dose Pharmacokinetics of Sofpironium Bromide after Intravenous and Dermal Administration (AL-6475-G)	Following intravenous administration to male rats, systemic exposure to sofpironium and BBI-401 was dose-related. No gender difference was noted. Sofpironium exhibited biphasic elimination from plasma with a terminal elimination $t_{1/2}$ ranging from 4.1 to 5.1 hr. Systemic exposure to BBI-4010 also increased with increasing doses of sofpironium bromide. The $t_{1/2}$ for BBI-4010 ranged from 2.3 to 5.0 hr. Following dermal administration of sofpironium bromide gel to rats with normal skin, systemic exposure to sofpironium was also dose-related. The bioavailability (F%) of sofpironium was very low, ranging from 1.6% to 2.1%. Following a single dermal administration of sofpironium bromide gel, 10% to the abraded skin of male rats, sofpironium absorption was more rapid and more bioavailable (F = 43.2%).
Single Dose Pharmacokinetics of ^{14}C-Sofpironium Bromide after Intravenous, Subcutaneous and Dermal Administration (Study AE-7665-G)	After a single sc administration to male rats, sofpironium-derived radioactivity was rapidly and completely absorbed (t_{max} = 0.25 hr) and then eliminated with a $t_{1/2}$ of 8.6 hr. The extent of absorption compared to the iv dose was 109.9%. In contrast to sc administration, ^{14}C-sofpironium-derived radioactivity was slowly and incompletely absorbed following dermal administration to male rats. The extent of absorption of ^{14}C-sofpironium-derived radioactivity was 6.1%.
Determination of the Plasma Concentrations of BBI-4000 and BBI-4010 after Administration of BBI-4000 to Minipigs by Multiple Routes (Study AI-6834-G)	Following a single 0.25 mg/kg iv administration of sofpironium bromide to male minipigs, the initial sofpironium bromide plasma concentration was 2195 ng/mL. Sofpironium bromide exhibited biphasic elimination from plasma, with a terminal elimination half-life ($t_{1/2}$) of 9.0 h. The maximum BBI-4010 plasma concentration (C_{max}) and time to reach the maximum concentration (T_{max}) were 12.6 ng/mL and 0.0167 h, respectively. BBI-4010 was eliminated with $t_{1/2}$ of 1.4 h. Following a single 0.25 mg/kg sc administration of sofpironium bromide to male minipigs, the sofpironium bromide plasma C_{max} and T_{max} values were 440 ng/mL and 0.0833 h, respectively, and the $t_{1/2}$ of sofpironium bromide was 4.2 h. The

	sofpironium bromide AUC was 330 ng·h/mL. The sofpironium bromide bioavailability (F) was 125.2%. The BBI-4010 plasma C_{max} and T_{max} values were 7.81 ng/mL and 0.917 h, respectively, and the $t_{1/2}$ of BBI-4010 was 3.0 h. Following a single dermal administration of sofpironium bromide gel 15% (IPM2 formulation) at a dose of 60 mg/kg to male minipigs, the sofpironium bromide bioavailability for dermal administration was 1.7%. The sofpironium bromide plasma C_{max} and T_{max} values were 47.7 ng/mL and 8.50 h, respectively, and $t_{1/2}$ of sofpironium bromide was 15.5 h. The sofpironium bromide $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ values were 1074 and 1093 ng·h/mL, respectively. The BBI-4010 plasma C_{max} and T_{max} values were 8.29 ng/mL and 24.0 h, respectively, and the $t_{1/2}$ for BBI-4010 was 14.0 h. The BBI-4010 $AUC_{0\text{-}t}$ was 219 ng·h/mL, respectively. The $AUC_{0\text{-}t}$ ratio of BBI-4010 against sofpironium bromide was 0.207.
Single Dose Plasma Concentrations of Sofpironium Bromide after Intravenous Administration (Study BBI-4000-NC-301)	There were no measurable sofpironium plasma concentrations in the 0.001 mg/kg dose group. The mean T_{max} value was 0.083 hr (5 min) for both 0.01 and 0.1 mg/kg groups and the $t_{1/2}$ values were similar between groups. Increases in C_{max} and $AUC_{0\text{-}t}$ were less than dose-proportional as a 10-fold increase in dose resulted in a 4.45-fold increase in C_{max}, and a 5.13-fold increase in $AUC_{0\text{-}t}$.
Distribution	
In vitro Plasma Protein Binding of ^{14}C-Sofpironium Bromide and its metabolite BBI-4010 by Ultrafiltration in Nonclinical Species and Human (Study M160106)	The in vitro plasma protein binding of ^{14}C -sofpironium and BBI-4010 was low in mouse, rat, rabbit, minipig, and human. Percentages of plasma protein-bound ^{14}C -sofpironium in vitro ranged from 36.3% to 39.1% for mouse, 30.3% to 34.2% for rat, 23.5% to 30.8% for rabbit, 28.5% to 31.5% for minipig, and 34.8% to 37.8% for human. Percentages of plasma protein-bound BBI-4010 in vitro ranged from 2.0% to 7.8% for mouse, 1.8% to 6.2% for rat, 0.0% to 11.2% for rabbit, 0.0% to 0.1% for minipig, and 2.3% to 3.7% for human. In addition, the in vitro plasma protein binding for both ^{14}C -sofpironium and BBI-4010 appeared to be independent of concentration.
In vitro Plasma Protein Binding Sofpironium Bromide by Equilibrium Dialysis (Study BBI-4000-NC-005)	Percentages of protein-bound sofpironium ranged from 37.3% to 54.4% for rat plasma, 71.0% to 85.1% for minipig plasma, and 70.5% to 75.7% for human plasma.

Feto-placental Transfer and Excretion in Milk after a Single Subcutaneous Administration of ^{14}C-BBI-4000 to Female Rats (Study AE-7674-G)	The transfer of ^{14}C-sofpironium and/or its metabolites across the placental barrier is low during both organogenesis (12th day of pregnancy) and late (18th day) pregnancy. Sofpironium or its metabolites were transferred into the milk after a single subcutaneous administration of 0.5 mg/kg to lactating rats on postpartum Day 10. Therefore, it is likely that nursing pups would be exposed to sofpironium and/or its metabolites via maternal milk. However, it might not be the case for this NDA since the systemic exposure is much lower for dermal administration which is the proposed clinical route for this application.
In vivo and In vitro Distribution Studies (Studies AE-7665-G, AE-7666-G, AE-7668-G)	^{14}C-Sofpironium -derived radioactivity was rapidly and extensively distributed into tissues following sc administration to male SD rats. The highest radioactivity concentrations were in the major organs of metabolism and excretion, and the lowest were observed in the cerebellum, and spinal cord. Sofpironium bromide is slowly (T_{max} 7-16 hr) and poorly absorbed (≤ 2.1% in rats and ~1.7% in minipigs) following dermal administration of a topical gel formulation. Sofpironium $t_{1/2}$ values were longer in rats (6-10 hr) and in minipigs (15 hr) following single dermal administration compared to subcutaneous administration. ^{14}C-Sofpironium -derived radioactivity was below the limit of detection in most tissues by 168 hr postdose indicating that it was not retained. The distribution of ^{14}C-Sofpironium to blood cells was low in vitro (<13%) across species (mouse, rat, rabbit, minipig and human blood), and in vivo in rats (≤32.5%) and minipigs (≤20.9%). Following sc administration of ^{14}C-Sofpironium bromide once daily for up to 14 days to male SD rats, the distribution of drug-derived radioactivity was similar to that observed following single dose administration. In most tissues, the tissue-to-plasma ratios at 24 hr after the last dose were similar to those at 24 hr after a single dose. The accumulation ratio (actual/predicted) was 3-fold or less in most tissues, suggesting that there was no unexpected accumulation in tissues upon repeated administration.

Metabolism	
In Vivo Metabolite Profiling of 14C-BBI-4000 in Rats and Minipigs (Study AE-7667-G)	Over 40 metabolites were identified or characterized in the biological samples. Most of the detected metabolites were generated by a combination of four types of reactions including deethylation by ester hydrolysis, generation of (b) (4) CYP-mediated hydroxylations, and desaturation resulting from dehydration of hydroxides. The major in vivo and in vitro sofpironium metabolite is BBI-4010. It is the only metabolite that exceeded greater than 10% of total drug exposure in plasma and/or urine of rats, minipigs and humans. Sofpironium was also found in 0-8 hr rat bile and accounted for 1.4% (0.4% of dose) of the biliary radioactivity; Sofpironium was not detected in minipig feces.
In vivo Sofpironium Metabolite Searching following Repeated Dermal Application of Sofpironium Bromide gel (IPM) to Humans (Study M160110)	Sofpironium bromide gel, 15% was applied to both axilla of six patients once daily before bedtime for 28 days. The metabolites detected in humans were considered to be generated by combinations of five reactions, deethylation by hydrolysis, (b) (4), hydroxylation by cytochrome P450, desaturation by dehydration of hydroxides, and glycine conjugation.
In Vivo Systemic Exposure Assessment to Metabolites in Plasma after Repeated Subcutaneous Administration of Sofpironium Bromide to Rats and Repeated Dermal Application of Sofpironium Bromide Gel to Humans (Study M160111)	The rat-to-human exposure ratio of BBI-4010, which was estimated to account for more than 10% of total drug exposure in humans, was 15.14.
In Vivo Search for Metabolites at the Site of Application after a Single Dermal Administration of Sofpironium Bromide Gel (IPM2) to Rats (Study M180106)	Following a single occlusive dermal administration of ^{14}C-sofpironium bromide IPM2 gel, 5% to rats, radioactivity in the skin was primarily associated with parent drug. The primary metabolite observed in the skin was BBI-4010, but its percentage was low (< 10%) even 72 hr after administration.
In Vivo Investigation of Chiral Inversion in Rats after a Single Subcutaneous Dose of Sofpironium Bromide (Study M190101)	Sofpironium diastereomers and sofpironium enantiomers are not present in rat plasma after a single sc administration of sofpironium and that chiral inversion of sofpironium does not occur in vivo in rats.

In vitro Metabolism of ^{14}C-Sofpironium Bromide in Hepatocytes, Liver Microsomes, Liver S9, and Skin S9 (Study M160105)	There were no human-specific metabolites observed in the study. Metabolite profiles of 14C-sofpironium in hepatocytes and/or liver microsomes were qualitatively similar across all species evaluated There were quantitative differences between rodents and non-rodents with respect to the extent of formation of minor hydroxylated metabolites. The metabolite profile of rabbit was between those of the rodent and non-rodent types. Almost no metabolites other than BBI-4010 were detected in rat or human skin S9; sofpironium was not metabolized to any significant extent by CYP450 in skin. All detected metabolites were generated by combination of 4 reactions, i.e., deethylation by hydrolysis, (b) (4), hydroxylation by CYP isoforms, and desaturation by dehydration of hydroxides.
In vitro Investigation of ^{14}C-Sofpironium Bromide Hydrolysis (Study AE-7671-G)	Following systemic absorption, sofpironium undergoes ester hydrolysis to form BBI-4010. This study showed that hydrolysis of sofpironium to produce BBI-4010 and (b) (4) was primarily a non-enzymatic (chemical) process.
Identification of Human Cytochrome P450 Isoforms Involved in the Metabolism of ^{14}C - Sofpironium Bromide (Study AE-7670-G)	The drug metabolizing enzymes primarily responsible for the oxidative metabolism of sofpironium are CYP2D6 and CYP3A4.
Excretion	
Absorption, Distribution, and Excretion of ^{14}C-BBI-4000 after a Single Administration to Rats by Multiple Routes (Study AE-7665-G)	After a single sc administration to male rats, the excretion of radioactivity up to 168 h after administration was 54.0% of dose in the urine, 45.0% in the feces. After a single occlusive dermal administration to male rats, the excretion of radioactivity up to 168 hr after administration was 0.7% of dose in the urine, 0.6% in the feces. The residual radioactivity in the dosing formulation remaining at the application site recovered at 24 h after administration was 90.2% of dose. The residual radioactivity in the application site of skin and the carcass (excluding the application site of skin) at 168 hr after administration was 5.2% and less than 0.05% of dose, respectively.

Determination of Radioactivity Concentrations in Plasma and Whole Blood and Excretion in Urine and Feces after a Single Subcutaneous Administration of 14C-BBI-4000 to Minipigs (Study AE-7666-G)	Sofpironium and/or its metabolites were also excreted in rat bile and underwent enterohepatic circulation. Following a single subcutaneous administration of ^{14}C-sofpironium bromide (0.25 mg/kg) to minipigs, drug-derived radioactivity is rapidly absorbed and excreted, almost equally, in urine and feces.
TK data from pivitol repeat dose toxicology studies: BBI-4000: Toxicity Study by Dermal Administration to CD-1 Mice for 13 Weeks / NJD0017 BBI-4000: Toxicity Study by Subcutaneous Administration to Sprague-Dawley Rats for 13 Weeks / NJD0011 BBI-4000: Toxicity Study by Subcutaneous Administration to Sprague-Dawley Rats for 26 Weeks / NJD0026	Sofpironium animal-to-human exposure multiples were 3- to 6- fold in mice (dermal), 3-to 10-fold in rats (subcutaneous) and 1- to 3-fold in minipigs (dermal) (See Section 19.3.1 for detailed calculations). <u>Mice at the NOAEL of 20% gel</u> sofpironium bromide: AUC_{0-t}: 751 (male) and 350 (female) ng·hr/mL C_{max}: 227 (male) and 41.9 (female) ng/mL T_{max}: 1-2 hour BBI-4010: AUC_{0-t}: 995 (male) and 605 (female) ng·hr/mL C_{max}: 59.4 (male) and 43.9 (female) ng/mL T_{max}: 8 hour Accumulation: No Systemic exposure: high inter-animal variation <u>Rat at the NOAEL of 1.5 mg/kg/day (male) and 5 mg/kg/day (female)</u> sofpironium bromide: AUC_{0-t}: 345 (male) and 1010 (female) ng·hr/mL C_{max}: 150 (male) and 434 (female) ng/mL T_{max}: 0.25-1 hour BBI-4010: AUC_{0-t}: 81.3 (male) and 480 (female) ng·hr/mL C_{max}: 36.8 (male) and 99.7 (female) ng/mL T_{max}: 0.25-2 hour Accumulation: No Systemic exposure increased with dose <u>Rat at the NOAEL of 0.5 mg/kg/day (male) and 5 mg/kg/day (female)</u> sofpironium bromide: AUC_{0-t} : 116 (male) and 1230 (female) ng·hr/mL; C_{max} : 56.5 (male) and 698 (female) ng/mL BBI-4100: AUC_{0-t} : 23.3 (male) and 479 (female) ng·hr/mL; C_{max} : 10.3 (male) and 100 (female) ng/mL Accumulation: Yes

BBI-4000: Toxicity Study by Dermal Administration to Minipigs for 39 Weeks / NJD0025	Systemic exposure generally increased with dose greater than dose proportionally <u>Minipigs at the NOAEL of 20% gel:</u> sofpironium bromide: $AUC_{0\text{-}t}$: 331 (male) and 161 (female) ng·hr/mL; C_{max} : 71.5 (male) and 36.3 (female) ng/mL BBI-4100 not quantifiable Accumulation: Yes
BBI-4000: A 28-Day Comparative Bridging Dermal Toxicity Study of Two Formulations in Gottingen Minipigs with a 14-Day Recovery Period (GLP)/ NY88DH	<u>Minipigs at the test dose level of 20% gel:</u> sofpironium bromide IPM: $AUC_{0\text{-}t}$: 218 (male) and 177 (female) ng·hr/mL C_{max}: 56.8 (male) and 43.3 (female) ng/mL T_{max}: 1 hour sofpironium bromide (b) (4) $AUC_{0\text{-}t}$: 39.6 (male) and 99.6 (female) ng·hr/mL C_{max}: 8.28 (male) and 20.8 (female) ng/mL T_{max}: 0.5 hour BBI-4010 IPM: $AUC_{0\text{-}t}$: 69.1 (male) and 66.3 (female) ng·hr/mL C_{max}: 6.86 (male) and 7.26 (female) ng/mL T_{max}: 2 hour BBI-4010 (b) (4) $AUC_{0\text{-}t}$: 38.4 (male) and 23.9 (female) ng·hr/mL C_{max}: 2.35 (male) and 4.51 (female) ng/mL T_{max}: 1 hour
BBI-4000 IPM Topical Gels: A 28-day Comparative Bridging Toxicity Study of Two Formulations by Dermal (Non-Occluded) Administration to Göttingen Minipigs Followed by a 21 Day Recovery Period / LD42FB	<u>Minipigs at the test dose level of 20% gel:</u> sofpironium bromide IPM1: $AUC_{0\text{-}t}$: 215 (male) and 454 (female) ng·hr/mL C_{max}: 36.3 (male) and 46 (female) ng/mL sofpironium bromide IPM2: $AUC_{0\text{-}t}$: 373 (male) and 308 (female) ng·hr/mL C_{max}: 53.5 (male) and 4188 (female) ng/mL BBI-4010 IPM1: $AUC_{0\text{-}t}$: 147 (male) and 13.8 (female) ng·hr/mL C_{max}: 13.6 (male) and 4.25 (female) ng/mL BBI-4010 IPM2: $AUC_{0\text{-}t}$: 89.2 (male) and 28.3 (female) ng·hr/mL C_{max}: 14.6 (male) and 36.7 (female) ng/mL
TK data from reproductive toxicology studies BBI-4000: Study for Effects on Fertility and Early	<u>Rat at the NOAEL of 10 mg/kg/day</u> sofpironium bromide: $AUC_{0\text{-}t}$: 8290 (male) and 2410 (female) ng·hr/mL

Embryonic Development in the Sprague Dawley Rat by Subcutaneous Injection Administration / CX29PL	C_{max}: 658 (male) and 1070 (female) ng/mL BBI-4010: AUC_{0-t}: 2860 (male) and 943 (female) ng·hr/mL C_{max}: 224 (male) and 134 (female) ng/mL
BBI-4000: Study for Effects on Embryo-Fetal Development in the Sprague Dawley Rat by Subcutaneous Injection Administration / JW40CS	<u>Rat at the NOAEL of 10 mg/kg/day</u> sofpironium bromide: AUC_{0-t}: 3730 ng·hr/mL C_{max}: 874 ng/mL BBI-4010: AUC_{0-t}: 1800 ng·hr/mL C_{max}: 175 ng/mL
BBI-4000: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit bynSubcutaneous Injection Administration / NJD0015	<u>Rabbit at the NOAEL of 2 mg/kg/day</u> sofpironium bromide: AUC_{0-t}: 1230 ng·hr/mL C_{max}: 1210 ng/mL BBI-4010: AUC_{0-t}: 461 ng·hr/mL C_{max}: 111 ng/mL
BBI-4000: Study for Effects on Pre- and Postnatal Development in the Sprague Dawley Rat by Subcutaneous Injection Administration /FP41VT	TK analysis was not performed
BBI-4000: A 13-Week Repeat Dose Subcutaneous Injection Toxicity Study in Juvenile Rats with a 4-week Recovery Period / 20144435	<u>Rat at the NOAEL of 10 mg/kg/day</u> sofpironium bromide: AUC_{0-t}: 1780 (male) and 1330 (female) ng·hr/mL C_{max}: 434 (male) and 631 (female) ng/mL BBI-4010: AUC_{0-t}: 723 (male) and 390 (female) ng·hr/mL C_{max}: 71.5 (male) and 97.0 (female) ng/mL
TK data from Carcinogenicity studies	
BBI-4000: Carcinogenicity Study by Subcutaneous Administration to Sprague-Dawley Rats for 104 Weeks (SD18VP)	<u>Rat at the NOAEL of 1.5 mg/kg/day (male) or 5.0 (female) mg/kg/day</u> sofpironium bromide: AUC_{0-t}: 489 (male) and 1380 (female) ng·hr/mL C_{max}: 168 (male) and 799 (female) ng/mL BBI-4010: AUC_{0-t}: 216 (male) and 604 (female) ng·hr/mL C_{max}: 52.1 (male) and 124 (female) ng/mL
BBI-4000 Topical Gel IPM: Carcinogenicity Study by Dermal Administration to CD-1 Mice for 104 Weeks (YV84GG)	<u>Mouse at the NOAEL of 20% gel on Day 182</u> sofpironium bromide: AUC_{0-t}: 228 (male) and 1260 (female) ng·hr/mL C_{max}: 18 (male) and 251 (female) ng/mL BBI-4010: AUC_{0-t}: 500 (male) and 450 (female) ng·hr/mL

	C_{max}: 30.7 (male) and 29.5 (female) ng/mL

5.5. Toxicology

5.5.1. General Toxicology

Repeat-Dose Toxicity Studies through Subcutaneous Administration

Subcutaenous (sc) GLP toxicology studies included 28-day, 13-week, and 26-week studies in rats.

Study title/ number: 28 Day Subcutaneous Toxicity and Toxicokinetic Study in Rats with a 14 Day Dose-Free Recovery Period / Study #BBI-4000-NC-103

Sprague-Dawley rats (12 sex/group except low dose at 8 sex/group) were given once daily sc injections of 0, 1, 5 or 10 mg/kg/day sofpironium bromide for 28 days. There were no treatment-related effects on mortality, systemic clinical signs, Functional Observation Battery (FOB) examinations, food consumption, urinalysis, ophthalmology, and organ weight.

Slightly lower body weights were noted in the 5 and 10 mg/kg/day male groups at the end of treatment period in comparison of the corresponding control group. Treatment-related effects on clinical signs, macroscopic and microscopic findings were limited to the injection sites, primarily in the 10 mg/kg/day male and female groups. These effects were associated with clinical pathology changes and were partially recovered at the end of the 14-day recovery period. Additionally, the pharmacologic effect of larger than normal pupil size was evident in rats treated with sofpironium bromide.

Based on the results of this study, the NOAEL of sofpironium bromide was considered to be 5 mg/kg/day for male and female rats.

Study title/ number: BBI-4000: Toxicity Study by Subcutaneous Administration to Sprague-Dawley Rats for 13 Weeks / Study #NJD0011

Subcutaneous doses of 0 (vehicle control; 0.9% sodium chloride), 0.5, 1.5 and 5 mg/kg/day sofpironium bromide were administered to Sprague-Dawley rats (10/sex/group) for 13 weeks. Clinical signs that are consistent with the anticholinergic pharmacologic activity of sofpironium bromide was noted. Body weight gain was decreased in high dose males (-19%) when compared to vehicle control males.

Treatment-related microscopic findings were noted at the injection site only. Focal needle tract-related tissue changes were observed at subcutaneous injection sites in all groups, including vehicle control. The findings included inflammatory cell infiltrates in the epidermis and dermis, mostly minimal to slight subcutaneous hemorrhages, subcutaneous inflammatory

cell infiltrates and subcutaneous fibrosis. Myofiber degeneration/ necrosis of the panniculus carnosus was also noted in high dose males and females.

The NOAEL of sofpironium bromide was identified as 1.5 mg/kg/day in males due to significant decreases in body weight gains noted in high dose males. The NOAEL was 5 mg/kg/day in females, the highest dose evaluated in the study.

Study title/ number: BBI-4000: Toxicity Study by Subcutaneous Administration to Sprague-Dawley Rats for 26 Weeks / Study #NJD0026
Subcutaneous doses of 0 (vehicle control; 0.9% sodium chloride), 0.5, 1.5 and 5 mg/kg/day sofpironium bromide were administered to Sprague-Dawley rats (10/sex/group) for 26 weeks. A dose dependent increase in incidence and severity of treatment-related effects on clinical signs consistent with the pharmacologic activity (anticholinergic agent) of sofpironium bromide was noted in this study.

Dose dependent decreases in body weight gain were observed in low, mid and high dose males (-11%, -16% and -23%, respectively) when compared to vehicle control males. Clinical chemistry parameters were assessed during weeks 13 and 26 for this study. Decreased plasma creatinine was noted in males at all dose levels on both week 13 and 26 when compared to controls. In addition, higher urinary pH levels were noted in males receiving 5 mg/kg/day on Weeks 13 and 26 when compared with controls.

Erythema and/or edema and eschar formation occurred intermittently at the injection sites predominantly in the high dose groups. Histopathological examination of the injection sites revealed degenerative changes affecting the panniculus muscle myofibers across all groups, including controls. These changes were consistent with low-grade local irritation produced by the repeated subcutaneous injections of the test item. The test article-related changes observed in the injection site of males and females treated with 5 mg/kg/day were of moderate severity.

The NOAEL of sofpironium bromide was identified as 5 mg/kg/day for females, the highest dose evaluated in this study. The NOAEL was 0.5 mg/kg/day for males based on extent of decreased body weight gain compared to vehicle control males.

Repeat-Dose Toxicity Studies through Dermal Administration
Dermal studies of sofpironium bromide (b) (4) gel were conducted at concentrations of up to 20% in sinclair miniature swine, for 13 weeks in CD-1 mice, and for 39-weeks in Göttingen minipigs. Repeat-dose dermal bridging studies were conducted in mice (14-day) and Göttingen minipigs (28-day) to evaluate new formulations with IPM (isopropyl myristate) instead of (b) (4) in the formulation. A bridging study was also conducted to assess the differences of two new formulations [IPM1 (synonymous with IPM, the commercial formulation) with (b) (4) citric acid concentration versus IPM2 with (b) (4) citric acid].

Study title/ number: A 28-day dermal toxicity and toxicokinetic in Sinclair miniature swine with a 14-day dose-free recovery / Study #BBI-4000-NC-002 (S12828)

Sofpironium bromide (b) (4) gel was topically administered to young Sinclair miniature swine at concentrations of 10% and 20% daily for 28 consecutive days. There were no treatment-related effects on clinical signs, physical examination, food consumption, body weights, clinical pathology, ophthalmology, ECG, papillary response, or respiratory rate. At necropsy, there were no gross, organ weight, or microscopic changes. Minimal erythema and/or edema was observed in both vehicle and sofpironium bromide-treated groups. The NOAEL of the study was considered to be 20% for sofpironium bromide (b) (4) gel.

Study title/ number: BBI-4000: Toxicity Study by Dermal Administration to CD-1 Mice for 13 Weeks / Study #NJD0017

Twelve mice/sex/group received daily unoccluded doses of sofpironium bromide (b) (4) gel containing 0% (vehicle), 5%, 10%, or 20% for approximately 23 hr/day. No treatment-related effects on mortality, clinical observations, dermal irritation, food consumption, hematology/ clinical chemistry parameters, or macroscopic/microscopic parameters were noted in this study. The NOAEL of the study was identified as 20% for sofpironium bromide gel, the maximum feasible concentration as well as the highest dose evaluated.

Study title/ number: BBI-4000: Toxicity Study by Dermal Administration to Minipigs for 39 Weeks / Study #NJD0025

Semi-occluded doses of 0% (vehicle), 5%, 10% or 20% sofpironium bromide gel were topically administered in Göttingen minipigs (4 sex/group) for 6 hr/day daily for 39 weeks. Erythema, edema and flaky skin was noted in all groups including the vehicle control groups. Decreases in reticulocyte count were also noted in all groups when compared to the corresponding pre-treatment values. The body weight adjusted spleen weights were higher in both 10% and 20% gel male and female groups when compared to the corresponding controls.

Microscopic findings of epidermal hyperplasia and/or epidermal ulceration were observed in the skin at the application site in both control and test article treated animals. This finding was possibly related to the semi-occlusive conditions. In addition, minimal sinus erythrocytosis/ erythrophagocytosis were observed in the left axillary lymph node in all groups including the control.

The NOAEL of the study was considered to be 20% for sofpironium bromide gel, the highest concentration tested.

General toxicology; additional studies

Study title/ number: 2-Week Dermal Bridging Toxicity and Toxicokinetic Study in CD-1 Mice with a 2-Week Recovery Period / Study #XW71GJ

The objective of the study was to evaluate a new sofpironium bromide formulation. The new formulation removed (b) (4) and replaced it with IPM. Four CD-1

mice/sex/group received unoccluded 23 hr/day dermal doses of the IPM formulation containing 0% (vehicle), 5%, 10%, or 20% sofpironium bromide for 15 days. There were no significant toxicity findings observed in the study. The NOAEL was established as 20% sofpironium bromide gel for both males and females. This study is reviewed in the below section.

Study title/ number: BBI-4000 (IPM): 2-Week Dose-Ranging Toxicity and Toxicokinetic (TK) Bridging Study by Dermal Administration to CD-1 Mice with a 2-Week Recovery Period
(b) (4) Study Number: XW71GJ

- Treatment of 20% sofpironium bromide gel in the IPM formulation was well tolerated in mice and the NOAEL was 20% gel for both males and females.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Doses:	0, 5%, 10%, and 20% sofpironium bromide IPM gel
Frequency of dosing:	Once daily for 14 days
Route of administration:	Topical
Formulation/Vehicle	IPM vehicle
Species/Strain:	CD-1 mice
Number/Sex/Group:	2/sex/group for main study groups 2/sex/group for receovery groups
Age:	3-4 months
Satellite groups:	3/sex/group for vehicle and 18 for test article groups
Unique study design:	None
Deviation from study protocol:	No deviations affect the conclusions

Observations and Results:

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	No test article-related effects
Dermal Observations	No test article-related effects
Body Weights / Food Consumption	No test article-related effects
Ophthalmoscopy *[*	No test article-related effects
ECG	No test article-related effects
Hematology	No test article-related effects
Clinical Chemistry	No test article-related effects

Urinalysis	No test article-related effects
Gross Pathology	No test article-related effects
Organ Weights	No test article-related effects
Histopathology Adequate battery: Yes/No	 Yes. No test article-related effects

Study title/ number: BBI-4000: A 28-Day Comparative Bridging Dermal Toxicity Study of Two Formulations in Gottingen Minipigs with a 14-Day Recovery Period / Study #NY88DH
The objective of the study was to compare two formulations of sofpironium bromide, (b) (4) gel and IPM gel. Sofpironium bromide (b) (4) gel or IPM gel at dose levels of 20% were applied topically to the dorsal/lateral area (10% of total body surface area) of Göttingen Minipigs (4/sex/group) once daily for 23 hours (± 1 hour), non-occluded, for up to 28 days.

Dermal observations of slight irritation were noted. Findings were similar between formulations and vehicles. One female minipig in the 20% sofpironium bromide IPM gel group was euthanized on Day 16 due to acute and severe skin ulceration at the dosing site. Reversible minimal dermal irritation was observed microscopically (minimal to slight epidermal exudates) in all groups. Severities were comparable between the two formulations. The mean combined gender plasma exposure was approximately 2-fold higher for the IPM formulation than for the (b) (4) formulation. There were no clear gender-related differences in exposure to either formulation. This study is reviewed in the below section.

Study title/ number: BBI-4000: A 28-Day Comparative Bridging Dermal Toxicity Study of Two Formulations in Gottingen Minipigs with a 14-Day Recovery Period (GLP) / NY88DH

- The treatment of sofpironium bromide topical gel in the (b) (4) or IPM vehicle for 23 hours/day to male and female minipigs was both tolerated and elicited similar levels of dermal irritations.
- One minipig given sofpironium bromide gel (IPM) 20% was euthanized on Day 16 because acute and severe skin ulceration was observed. Due to the leftover group size of n=1, the value of this study is limited.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Doses:	0 ((b) (4) vehicle), 0 (IPM vehicle), 20% sofpironium bromide (b) (4) gel, 20% sofpironium bromide IPM gel
Frequency of dosing:	Once daily for 28 days
Route of administration:	Topical

Formulation/Vehicle:	Gel / (b) (4) or Isopropyl Myristate (IPM) vehicle
Species/Strain:	Gottingen Minipigs
Number/Sex/Group:	2/sex/group
Age:	4-5 months
Satellite groups:	None
Unique study design:	2/sex/group instead of 4/sex/group
Deviation from study protocol:	No deviations affect the conclusions

Observations and Results: changes from control

Parameters	Major findings
Mortality	No test article-related effects; One minipig given sofpironium bromide gel (IPM) 20% was euthanized on Day 16 because acute and severe skin ulceration was observed.
Clinical Signs	No test article-related effects
Dermal Observations	Slight erythema in all groups
Body Weights / Food Consumption	No test article-related effects
Ophthalmoscopy *[*	No test article-related effects
ECG	No test article-related effects
Hematology	No test article-related effects
Clinical Chemistry	No test article-related effects
Urinalysis	No test article-related effects
Gross Pathology	No test article-related effects
Organ Weights	No test article-related effects
Histopathology Adequate battery: Yes/No	Yes. Slight dermal irritation was observed in both gel formulations.

Study title/ number: BBI-4000 IPM Topical Gels: A 28-day Comparative Bridging Toxicity Study of Two Formulations by Dermal (Non-Occluded) Administration to Göttingen Minipigs Followed by a 21 Day Recovery Period / Study # LD42FB

This comparative toxicity study compared the systemic and local toxicity and TK of two formulations of sofpironium bromide IPM gel administered via unoccluded dermal dosing for 23 hr/day for 4 consecutive weeks in Göttingen minipigs. Recovery from any effects was evaluated during a 21-day dose-free recovery period.

The two sofpironium bromide gel formulations, IPM1 (synonymous with IPM) and IPM2, were identical with the exception of citric acid content; (b) (4) (to-be-marketed formulation) and (b) (4) for the IPM1 and IPM2 formulations, respectively. Sofpironium bromide gels (0.43

mL/kg/day) were applied at a concentration of 20% to approximately 10% BSA. Control animals received both vehicles (IPM1 vehicle or IPM2 vehicle) over a fixed dose area of 200 cm^2 per site.

The main finding of the study was reversible irritation at dose site. The mean incidence and severity was similar between formulations and without gender difference. Assessment of immunotoxicologic endpoints (CD79a, CD3, CD8 and Anti-Smooth Muscle Actin markers) and naive skin samples from all surviving minipigs demonstrated that application of the sofpironium bromide IPM gel formulations (IPM1 and IPM2) did not elicit an acute sensitization response. Group mean systemic toxicokinetics were similar for both formulations and there were no statistically significant sex-related differences for either formulation. This study is reviewed in the below section.

Study title/ number: BBI-4000 IPM Topical Gels: A 28-day Comparative Bridging Toxicity Study of Two Formulations by Dermal (Non-Occluded) Administration to Göttingen Minipigs Followed by a 21 Day Recovery Period/ LD42FB

- Treatment of 20% sofpironium bromide IPM1 gel or IPM2 gel was both tolerated in minipigs and the major finding was reversible irritation at dosing sites.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Doses:	0 (IMP1 vehicle), 0 (IPM2 vehicle), 20% sofpironium bromide IPM1 gel, 20% sofpironium bromide IPM2 gel
Frequency of dosing:	Once daily for 28 days
Route of administration:	Topical
Formulation/Vehicle:	Gel / IPM1 containing 0.001% citric acid or IPM2 containing vehicle
Species/Strain:	Gottingen Minipigs
Number/Sex/Group:	2/sex/group for vehicle groups 4/sex/group for test article treatment groups
Age:	3-4 months
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No deviations affect the conclusions

Observations and Results:

Parameters	Major findings
Mortality	No test article-related effects. One female receiving 20% sofpironium bromide IPM1 gel was euthanized on Day 14 due to the severity of the reactions at the dose site.
Clinical Signs	No test article-related effects
Dermal Observations	Erythema, edema, eschar formation, fissuring and desquamation in all groups
Body Weights / Food Consumption	No test article-related effects
Ophthalmoscopy *[*	No test article-related effects
ECG	No test article-related effects
Hematology	No test article-related effects
Clinical Chemistry	No test article-related effects
Urinalysis	No test article-related effects
Gross Pathology	No test article-related effects
Organ Weights	No test article-related effects
Histopathology Adequate battery: Yes/No	Yes. Microscopic findings of sebaceous gland hyperplasia, hyperkeratosis, ulceration and inflammation at the dose sites were observed in all groups.

5.5.2. Genetic Toxicology

Sofpironium bromide was not genotoxic in all the studies tested, including Ames assay, chromosomal aberration assay in human peripheral blood lymphocytes, and in vivo micronucleus assay in rats.

Study title/ number: Bacterial reverse mutation assay / Study no.: BBI-4000-NC-007
Sofpironium bromide was tested in the Bacterial Reverse Mutation Assay using Salmonella typhimurium tester strains TA98, TA100, TA1535 and TA1537 and Escherichia coli tester strain WP2 uvrA in the presence and absence of Aroclor-induced rat liver S9. In the preliminary toxicity assay, the maximum dose tested was 5000 µg per plate. This dose was achieved using a concentration of 50 mg/mL and a 100 µL plating aliquot. The dose levels tested were 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333 and 5000 µg per plate. Neither precipitate nor background toxicity was observed.

Based on the findings of the preliminary assay, the dose levels selected in the definitive mutagenicity assay were 50, 150, 500, 1500 and 5000 µg per plate. Neither precipitate nor

background toxicity was observed. No positive mutagenic responses were noted in the test article group with any of the tester strains in either the presence or the absence of S9 activation. Under the conditions of this study, sofpironium bromide was negative in the Bacterial Reverse Mutation assay.

Study title/ number: Mammalian chromosome aberration assay in human peripheral blood lymphocytes / Study no.: BBI-4000-NC-003
Sofpironium bromide was tested in the chromosome aberration assay using human peripheral blood lymphocytes (HPBL) in both absence and presence of an Aroclor-induced rat liver S9 metabolic activation system. The doses tested in the preliminary toxicity assay ranged from 0.047 to 470 µg/mL (1 mM). The dose levels selected for analysis of chromosome aberrations in the definitive assay were 50, 150, 350, and 470 µg/mL. Under the conditions of the assay, sofpironium bromide was negative for the induction of structural and numerical chromosome aberrations in the in vitro mammalian chromosome aberration assay. Substantial toxicity was not observed at any dose tested. No significant or dose dependent increases in the frequency of cells with structural or numerical chromosomal aberrations were observed in the test article group with or without S9.

Study title/ number: In vivo micronucleus assay in rats / Study no: BBI-4000-NC-104 and 105
Sofpironium bromide was evaluated for its clastogenic activity by detecting micronuclei in polychromatic erythrocyte (PCE) cells in rat bone marrow. The rats were administered 2 subcutaneous injections (2 dose sites) of sofpironium bromide at a dose volume of 10 mL/kg.

In the initial dose range finding (DRF) assay, the maximum dose tested was 500 mg/kg. The dose levels tested were 125, 250 or 500 mg/kg administered to groups of 3 animals/sex each. No mortality was noted in the study. In another repeat DRF assay, the dose levels tested were 750, 1000, 1500 or 2000 mg/kg administered to groups of 3 animals/sex each. Mortality was observed at all dose levels. Based upon the results of the two DRF studies, the high dose for the definitive assay was 550 mg/kg, which was estimated to be the maximum tolerated dose (MTD).

In the definitive assay, sofpironium bromide were tested at dose levels of 115, 225 or 550 mg/kg. Since no differences in the clinical signs of toxicity were observed between the sexes in the DRF assays, only male rats (10/group) were used in the definitive assay. Bone marrow cells [polychromatic erythrocytes (2000 PCEs/animal)] were examined microscopically for the presence of micronuclei (micronucleated PCEs; MnPCEs) and statistical analysis of data was performed.

Treatment with sofpironium bromide did not induce a significant increase in the incidence of PCE at any dose or sampling time point, indicating no bone marrow toxicity. Under the conditions of this study, sofpironium bromide was concluded to be negative in the in vivo rat micronucleus assay.

Other Genetic Toxicity Studies
None.

5.5.3. Carcinogenicity

In a 2-year dermal mouse carcinogenicity study, sofpironium bromide topical IPM gel was administrated daily to CD-1 mice unoccluded 23 hr/day. Doses evaluated in this study included 0% (vehicle), 5%, 10% or 20% sofpironium bromide gel. Due to increased mortality, dosing was stopped when the number of surviving animals by gender reached 20. Dosing was stopped for the male animals that were treated with 10% or 20% gel on Week 92 or Week 78, respectively. In addition, the treatment was terminated at the end of Week 90 for the 20% gel male group. All other groups continued dosing until the end of the study. The termination criteria for male and female mice in this study received the Executive Carcinogenicity Assessment Committee (ECAC) concurrence. No sofpironium bromide treatment-related tumor findings were noted in this study.

In a 2-year subcutaneous rat carcinogenicity study, sofpironium bromide was subcutaneously administrated to Sprague-Dawley rats daily for 104-weeks [males (0, 0.3, 0.75, 1.5 mg/kg/day) and females (0, 0.5, 1.5, 5.0 mg/kg/day)]. No sofpironium bromide treatment related tumor findings were noted in this study. Subcutaneous sofpironium bromide administration caused injection site inflammation/degenerative changes associated with irritation. In females given 5.0 mg/kg/day, epidermal hyperplasia was noted but considered to be attributed to a local irritant effect of daily repeated subcutaneous injection of sofpironium bromide. These local injection site effects are not clinically relevant since the clinical use will be topical administration.

Refer to Appendix 19.3.3 for full carcinogenicity study reviews.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Study title/ number: BBI-4000: Study for Effects on Fertility and Early Embryonic Development in the Sprague Dawley Rat by Subcutaneous Injection Administration / CX29PL
Three groups of 22 male and 22 female Sprague Dawley Crl:CD(SD) rats received sofpironium bromide at doses of 1, 3 or 10 mg/kg/day by subcutaneous injection. Males were treated daily for four weeks before pairing, throughout pairing until termination after a minimum of six weeks treatment. Females were treated daily for two weeks before pairing, throughout pairing, and until Day 7 after mating.

There was one mortality on Day 1 in the 1 mg/kg/day male group. The cause of death was not identified. Dose-dependent erythema, eschar and edema were noted at the injection sites in

both males and females, but to a lesser extent in females. At necropsy, scabbing and dark areas on the subcutaneous surface at injection sites were observed in the 10 mg/kg/day male group.

A decrease of the overall body weight gains (Day 1-46) were noted in males in all test article-treated groups, as 79%, 65% and 67% of the corresponding control value at 1, 3 and 10 mg/kg/day, respectively. In females, there was no effect of sofpironium bromide on body weights during gestation period. However a dose-dependent decrease in body weight gains (up to 72%) was noted on Day 1-15 before pairing. Slight decreases in food consumption were also observed with sofpironium bromide treatment.

A decrease in cauda epididymis weight (<10%) in the 10 mg/kg/day group was noted when compared to the corresponding control, but it was not dose dependent. A slight decrease in the organ weight of epididymides, prostate, and seminal vesicles were also noted in the same group. However, it was not statistically significant different. There were no significant treatment-related effects on male fertility index and maternal reproductive parameters, including numbers of corpora lutea, implantation, pre- and postimplantation loss, resorptions (early or late) and numbers of live embryos.

The NOAEL of sofpironium bromide on male and female fertility and early embryonic development was considered to be 10 mg/kg/day.

Embryo-Fetal Development
Study title/ number: BBI-4000: Study for Effects on Embryo-Fetal Development in the Sprague Dawley Rat by Subcutaneous Injection Administration / JW40CS
Three groups of 20 female Sprague Dawley rats received sofpironium bromide at doses of 1, 3 or 10 mg/kg/day by daily subcutaneous injection from gestation day (GD) 6 to 17 after mating. Animals were sacrificed on GD 20 after mating for reproductive assessment and fetal examination.

Scabs/eschar formation and identified dark areas were observed on the subcutaneous surface of the skin at injection site in the animals of 10 mg/kg/day treatment group. A slight decrease in body weight gain and food consumption was observed in all treatment groups when compared to control.

The incidence of ossified cervical vertebral centra, thinning of diaphragm with liver protrusion, liver hemorrhages was slightly increased at 10 mg/kg/day (see table below).

Table 6: Findings in Fetal Pathology

Findings	Incidence (Fetuses / Litters)			
	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day

Ossified cervical vertebral centra	3/2	0/0	1/1	6/5
Thinning of diaphragm with liver protrusion	1/1	2/2	1/1	5/5
Liver hemorrhages	1/1	2/2	4/3	6/3

At 10 mg/kg/day there was a higher incidence of ossified cervical vertebral centra (fetal/litter incidence 6/5, control incidence 3/2), thinning of diaphragm with liver protrusion (fetal/litter incidence 5/5, control incidence 1/1) and liver hemorrhages (fetal/litter incidence 6/3, control incidence 1/1) compared to concurrent control. The incidence of ossified cervical vertebral centra was within historical control ranges (maximum fetal/litter incidence 12/8) and the litter incidence of liver hemorrhages was within historical control range (maximum fetal/litter incidence 5/4). As fetuses within a litter share the same genetic and environmental conditions the litter becomes the more appropriate unit of assessment for malformations and therefore these differences within the historical litter incidence are not attributed to an adverse effect of treatment. The diaphragm thinning with liver protrusion as observed at an incidence of 5 offspring within 5 litters was above the historical control data which was 2 fetuses within 2 litters. This finding is not related to the adverse malformation of diaphragmatic hernia, it does not affect postnatal survival, growth or development and can be observed in adult animals of this strain therefore it is not considered to be adverse.

Major vessel/ heart abnormalities (2 fetuses), dilated ureters (2 fetuses/2 litters), or a slight increased incidence of small lobe of thyroid (fetal/litter incidence 3/3) were observed at 3 mg/kg/day. However, these findings were either within historical control or not associated with a dose-related trend.

The NOAEL for maternal toxicity and embryo-fetal development was identified as 10 mg/kg/day for sofpironium bromide.

Study title/ number: BBI-4000: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Subcutaneous Injection Administration / NJD0015
Three groups of 20 New Zealand female rabbits received sofpironium bromide at doses of 0.4, 2 or 10 mg/kg/day by daily subcutaneous injection from GD 6 to 19 after mating. Animals were sacrificed on GD 29 after mating for reproductive assessment and fetal examination.

One animal in the 0.4 mg/kg/day group was sacrificed on GD 14. Erythema and bruising were noted at the injection site in all groups. Edema was observed at the injection site in the 10 mg/kg/day group. Dilated pupils and pinna(e) cold or hot to touch were observed with all dose levels of sofpironium bromide treatment.

Dose-dependent decreases in body weight gains were observed in test article-treated animals during the gestation period (see table below). There were 62% of the control body weight gains in the 0.4 mg/kg/day group and 37% of control in the 2 mg/kg/day group. Body weight loss was recorded at 10 mg/kg/day in comparison of control animals. Following the cessation of sofpironium bromide treatment, body weight gains recovered at 155%, 236% or 200% of control weight gain at 0.4, 2 or 10 mg/kg/day, respectively.

Table 7: Maternal Body Weight Changes

	0 mg/kg/day	0.4 mg/kg/day	2 mg/kg/day	10 mg/kg/day
Body weight change (Day 6-20) (kg)	0.16	0.10	0.06	-0.06
% of control	-	62%	37%	-37%
Body weight change (Day 20-29)(kg)	0.11	0.17	0.26	0.22
% of control	-	155%	236%	200%

Dose dependent decreases in food consumption were observed throughout the dosing period in all treatment groups, being 89%, 75% and 47% of the control value at 0.4, 2 and 10 mg/kg/day, respectively. After cessation of treatment (from Day 20 of gestation), recovery was observed and food intake was significantly higher than the control in all sofpironium bromide-treated groups, at 123%, 134% and 136% of the control value at doses of 0.4, 2 or 10 mg/kg/day, respectively.

Table 8: Maternal Food Consumption Changes

	0 mg/kg/day	0.4 mg/kg/day	2 mg/kg/day	10 mg/kg/day
Food consumption (Day 6-19) (g)	127	113	95	60
% of control	-	89%	75%	47%
Food consumption (Day 20-29)(g)	98	121	131	133
% of control	-	123%	134%	136%

There was a slight decrease in pregnancy rate noted with the sofpironium bromide-treated groups. However, based on study design for embryo-fetal development studies and the dosing period from GD 6, this decrease is not considered to be test article-related.

There was also an increase in post-implantation loss in the 2 mg/kg/day and 10 mg/kg/day groups resulting from an increased incidence of late resorptions in these two groups due to maternal toxicity observed in these groups (see table below).

Table 9: Reproductive Assessment

Reproductive Assessment	0 mg/kg/day	0.4 mg/kg/day	2 mg/kg/day	10 mg/kg/day
# animals not pregnant	1	2	5	3
# animals pregnant on Day 29	21	19	17	19
Corpora Lutea	10.5	11.2	11.1	9.9
Implantations	9.5	9.9	10.4	9.4
Early resorption:	0.2	0.4	0.2	0.3
Late resorption:	0.1	0.0	0.4	0.4
Live young male	4.8	5.4	4.9	4.2
Live young female	4.4	4.1	4.8	4.4
Live young total	9.2	9.5	9.7	8.5
Sex ratio (% M)	52.5	57.4	51.2	49.3
Pre-implantation loss	11.3	12.0	7.7	7.2
Post- implantation loss	4.2	3.7	5.5	8.9

Increased incidence of minor skeletal abnormalities and delayed/incomplete ossification/ unossified was noted in the 0.4 mg/kg/day group and 10 mg/kg/day group. In addition, head abnormalities such as subdural hemorrhage or dilated interventricular foramen were noted in the 2 mg/kg/day group and 10 mg/kg/day group (see table below). However, the incidence of major and minor abnormalities and skeletal variants did not establish a dose relationship to maternal sofpironium bromide administration.

Table 10: Fetal Pathology

	Findings (fetuse/litter)			
	0 mg/kg/day	0.4 mg/kg/day	2 mg/kg/day	10 mg/kg/day
Minor skeletal abnormalities	10/8	21/8	8/5	19/9
Cranial unossified areas	0/0	2/2	0/0	3/2
Partially fused sternebrae	0/0	1/1	0/0	3/2
Costal cartilage hole in xiphoid	0/0	0/0	0/0	2/1
Delayed/incomplete ossification /unossified				
Cranial-large anterior fontanelle	0/0	2/2	0/0	2/2
Head abnormalities (fixed visceral)	1/1	0/0	5/5	2/2

Based on the results of the study, the NOAEL for embryo-fetal development was identified as 2 mg/kg/day based on the extent of postimplantation loss noted at 10 mg/kg/day. Since no treatment-related malformations were noted in this study, the fetal malformation NOAEL was 10 mg/kg/day. A NOAEL for maternal toxicity could not be established based on the results of this study including a significant decrease in body weight gain for all treatment groups.

Prenatal and Postnatal Development
Study title/ number: BBI-4000: Study for Effects on Pre- and Postnatal Development in

the Sprague Dawley Rat by Subcutaneous Injection Administration / FP41VT
The potential of sofpironium bromide (an anticholinergic) related effects on pre- and postnatal development was assessed following daily subcutaneous administration from GD 6 after mating until lactation day (LD) 20 in the Sprague Dawley rat at doses of 1, 3 or 6 mg/kg/day. Animals in the F1 and F2 generation were not directly dosed.

Scabs/eschar formation was observed at the injection sites in all sofpironium bromide treated F0 groups. Slight decreases in body weight gains and food consumption were observed in the 6 mg/kg/day F0 female groups. During gestation period, the animals in the 6 mg/kg/day group had lower overall body weight gains at 83% of the control value. During lactation period, the overall body weight gain for animals at 6 mg/kg/day was significantly higher than the control group at 133% of the control value (see table below).

Table 11: Maternal Body Weight Changes

	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	6 mg/kg/day
Body weight change (g) (Gestation Day 6-20) (% of control)	113 (-)	108 (96%)	105 (93%)	94 (83%)
Body weight change (g) (Lactation Day 1-21)(% of control)	27 (-)	22(81%)	28 (96%)	36 (133%)

Natural delivery and litter observations
Offspring body weights on Day 1 for males and females were similar to Controls at all dose levels. The F1 offspring body weight gains of both males and females during Days 1-21 of age were slightly lower (<10%) at 3 or 6 mg/kg/day than the control values (see table below).

There was no treatment-related effect observed on gestation length, with all females being within the expected range of 22 to 23 days at parturition. Gestation index was 100% in all study groups.

There was no effect of sofpironium bromide treatment on mean number of implantations, numbers of live young, offspring survival, litter size or survival indices. Mean sex ratio (% male) was similar across all groups and was unaffected by treatment.

Table 12: Summary of Reproductive Performance

F0 generation female:	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	6 mg/kg/day
Pregnant rate	100%	100%	100%	100%
Delivered litter	22	22	22	22
Duration of gestation	22-23	22-23	22-23	22-23
Gestation index	100%	100%	100%	100%
Live birth index	98.5	97.2	99.2	97.5
Post implantation survival index	97.2	93.0	96.9	94.1
F1 generation litters:	**0 mg/kg/day**	**1 mg/kg/day**	**3 mg/kg/day**	**6 mg/kg/day**
Viability index	99.1	97.7	98.9	99.7
Lactation index	99.5	99.1	100	99.4
Sex ratio (postpartum Day 1) (postpartum Day 21)	50.3 49.8	44.0 44.3	53.3 50.4	56.4 52.7
Litter size (postpartum Day 1) (postpartum Day 21)	16.1 10.0	15.6 9.8	16.2 9.9	15.0 9.9
Pup weight (Male/Female) (postpartum Day 1) (postpartum Day 21)	 6.7/6.3 51.2/49.7	 6.7/6.4 51.5/49.7	 6.5/6.1 49.1/46.7	 6.6/6.2 47.1/45.5

F1 Litter Responses

There were three unscheduled F1 mortalities, one female in the control group, one male and one female from an F0 female receiving sofpironium bromide at 3 mg/kg/day.

The overall (Day 1-81) body weight gains of the F1 males derived from test article treated F0 females were slightly higher (<10%) than that of the control group.

Table 13: F1 Offspring Body Weight Changes

Body weight changes (g)	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	6 mg/kg/day
Male: Day 1-81	408	438 (107%)	448 (110%)	435 (107%)
Female: Day 1-39 before pairing Day 0-20 gestation Day 1-14 lactation	 150 159 32	 161 169 32	 155 168 33	 156 165 32

There were no test article-related effects on F1 motor activity of the females. Based on high and low beam-break scores, F1 males derived from F0 females given 6 mg/kg/day had lower activity levels when compared to the corresponding control group. However, the values were within the historical range and may reflect normal variation.

There were no test article-related effects on F1 learning and memory as assessed by the Morris maze test. There were no test article-related effects on F1 sexual maturation, as assessed by balano-preputial separation and vaginal opening. There were no test article-related

effects on pre-coital interval, mating performance, fertility or gestation index, or gestation length. Macropathology examination of the selected F1 offspring did not indicate test article-related effects.

F2 Litter Responses

The mean number of implantations, numbers of live young, offspring survival, litter size or survival indices, and mean sex ratio of F2 did not indicate any test article-related effects. The clinical signs and body weights of the F2 litters as well as macropathology examination of the F2 litters did not indicate any test article-related effects. F2 litters were terminated after 14 days of observation.

Based on the results of the study, the NOAEL for maternal (F0) treatment from GD 6 to LD 20 was considered to be 3 mg/kg/day. The NOAEL for the pre- and postnatal survival, and growth of the F1 and F2 offspring, and neurobehavioural development and reproductive performance and maturation of the F1 offspring, was considered to be 6 mg/kg/day.

Juvenile Animal Study

Study title/ number: BBI-4000: A 13-Week Repeat Dose Subcutaneous Injection Toxicity Study in Juvenile Rats with a 4-week Recovery Period /Study no. : 20144435

Sofpironium bromide was administrated to juvenile Sprague-Dawley rats via subcutaneous injection at doses of 0 (Control), 0.5, 1.5, or 5 mg/kg/day from Postnatal Day (PND) 7 through 98.

Sofpironium bromide-related microscopic findings were limited to the administration site in males and females at 5 mg/kg/day. These microscopic findings included mononuclear cell inflammation and degeneration/necrosis of panniculus carnosus. Low numbers of inflammatory infiltrates were often observed in the subcutaneous tissue however, they occurred at the same incidence and severity as the controls. Atrophy of the muscle fibers was observed in the panniculus carnosus in one treated male and regeneration of the muscle fibers was observed in one treated female. None of the findings were observed at the end of the recovery period. Based on these results, the NOAEL of the study was considered to be 5 mg/kg/day.

5.5.5. Other Toxicology Studies

In vitro Bovine Corneal Opacity and Permeability Assay (Study HK64MS, GLP)

The objective of the study was to assess the potential of sofpironium bromide IPM gel vehicle (0%) and 20% concentration to cause ocular toxicity. Under the condition of the study, sofpironium bromide gel, 20% was predicted to have a classification of Category 1 for ocular irritation, indicating its potential to cause eye damage.

Local Lymph Node Assay in CBA/Ca Mice: Pooled Method (Study MD76QQ, GLP)

Four groups (4 females/group) of CBA/Ca mice received 50 µL (25 µL per ear) of sofpironium

bromide IPM gel at concentrations of 0% (vehicle), 5%, 10%, or 20% once daily for three consecutive days. There were no deaths or signs of systemic toxicity during the study. No visual signs of local skin irritation. Each concentration of sofpironium bromide gel demonstrated a Stimulation Index of <3.0 and therefore was considered to be non-sensitizing under the conditions of the test.

Buehler Sensitization Test in Guinea Pigs (Study BBI-4000-NC-004, GLP)

This study was conducted to determine the potential of 10% sofpironium bromide (b) (4) gel to produce a dermal sensitization reaction in guinea pigs. Under the conditions of the assay, sofpironium bromide (b) (4) gel, 10% did not cause a sensitization reaction. Mild erythema was noted with treatment of sofpironium bromide (b) (4) gel, 10%.

Spectroscopy Scans of Sofpironium Bromide (b) (4) Gel 5% (Study BBI-4000-DP-001, Non-GLP)

A spectroscopic scan from 190 – 700 nm was performed. Sofpironium bromide (b) (4) gel 5% had absorption in the range of 190 to 240 nm. Therefore, sofpironium bromide (b) (4) gel, 5% does not absorb between 290 and 700 nm of the electromagnetic spectrum.

Light Absorption Test for Sofpironium Bromide IPM Gel 15% (Study PF16C163(r.1), Non-GLP)

A spectroscopic scan from 190 – 700 nm was performed. The maximal absorption range was 190-240 nm for the sofpironium bromide IPM gel, 15%. The maximal absorption range was 190-280 nm for the vehicle. Neither of them has a Molar Extinction Coefficient greater than 1000 L mol^{-1} cm^{-1}. Therefore, the drug product, sofpironium bromide IPM gel, 15%, cannot be photoactivated and cannot elicit phototoxicity.

Excipients:

There are no novel excipients in the proposed product. It is noted that nonclinical studies conducted during early product development used (b) (4) formulation of sofpironium bromide and they are different from the to be marketed formulation with IPM formulation. The mouse carcinogenicity study was conducted with the final clinical formulation. Bridging studies were also conducted and did not identify any differences in toxicity profiles of sofpironium bromide.

Impurities

During the development program, sofpironium bromide and potential impurities in the investigational drug product were evaluated using two in silico computational quantitative structure-activity relationship systems (Derek Nexus and CASE Ultra), database literature searches and an expert review of in silico results. These assessments did not identify any structure-activity alerts or evidence of genotoxicity for any compound identified in the intended commercial sofpironium bromide IPM gel drug product.

In vitro bacterial mutagenicity (Ames) and chromosomal aberration assays were conducted for the (b) (4)

[redacted] (Studies KF18212; KF18211; KF18214; KF18213) and an in vivo 4- week repeat dose general toxicity study was conducted in SD rats (Study KF18215). Neither [redacted] showed any genotoxic or clastogenic potential in the in vitro studies. In the in vivo 4-week study in rats, there were no differences in the toxicity profiles caused by the spike of the [redacted] at doses of up to [redacted]% ([redacted] mg/kg/day of each impurity). The NOAEL for sofpironium bromide containing the [redacted]s was [redacted]mg/kg/day.

Three potential drug [redacted] were evaluated in a battery of genetic toxicity assays in order to qualify them based on ICH Q3B(R2) guideline threshold limits ([redacted]% for a 174 mg/day dose). The compounds [redacted] did not exhibit any mutagenic potential in Ames assays nor show evidence of any potential to induce chromosomal aberrations in human peripheral blood lymphocytes in vitro. A 28-day repeat-dose dermal toxicity and TK study of sofpironium bromide gel, 5% and 20% gel compared to the same gel spiked with [redacted]% of each of the [redacted] and [redacted] degradants (up to [redacted] mg/kg/day per impurity) was conducted in in SD rats. No differences in toxicity or TK profiles were identified between groups regardless of the presence or absence of the degradants. An additional 28-day repeat dose dermal administration toxicity and TK study was conducted in CD-1 mice to further qualify [redacted] and to assess an additional degradant, [redacted] Following 28 consecutive days of unoccluded 23 hr/day dermal administration of sofpironium bromide gel, 20% or sofpironium bromide gel, [redacted] there were no between-group differences in toxicity profiles. The results of these studies support qualification of [redacted] at levels of [redacted] in the sofpironium bromide gel drug product.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking the approval of for sofpironium bromide gel, 15% for the topical treatment of hyperhidrosis in subjects 9 years of age and older. Sofpironium bromide is a new molecular entity (NME) and belongs to the class of anticholinergic drugs. It is a selective, competitive inhibitor of the muscarinic receptor type 3 (M3), which is the predominant receptor in sweat glands. Eleven studies have assessed PK and/or pharmacodynamic (PD) parameters across the three formulations. The clinical pharmacology of sofpironium bromide gel 15% has been evaluated in a total of 6 studies in adults and 2 studies in pediatric subjects using the intended commercial to-be-marketed formulation (IPM1 formulation). The list of all clinical pharmacology related studies is mentioned in Appendix 16.4.0(Table 16.4.1.1).

Systemic exposure to sofpironium appeared to increase in an approximately dose-proportional manner between the 5% and 15% gel concentrations, indicating that applying a more concentrated gel increased exposure. However, inter-subject variability of PK parameters was extremely high. When combined with results from the repeat dose studies, steady state was likely reached within the first 24 hours. Across the program, systemic exposure of sofpironium and metabolite BBI-4010 was typically low following the first dose (Day 1) and subsequent PK assessment visits, and accumulation was not observed on multiple dosing.

In the 21-day maximal use PK (MUPK) study (Study BBI-4000-CL-102), a 3-fold increase over the proposed therapeutic dose (applied to axillae, ventral thighs, and palms) was studied in subjects with hyperhidrosis and was well tolerated. A single dose that was 6-fold higher than the proposed therapeutic dose (applied to the axillae, lateral side of the upper arms, ventral side of the thighs, and central abdomen under occlusion; 1038 mg of sofpironium bromide) was well tolerated in healthy adult subjects, despite a 2- to 4-fold increase in exposure (Studies BBI-4000-CL-106 and BBI-4000-CL-109).

Although PK was quite variable, there was no discernable pattern demonstrating a difference in exposure in healthy subjects versus in subjects with hyperhidrosis. The effect of renal and hepatic impairment on the pharmacokinetics of sofpironium is unknown and was not assessed.

The drug metabolizing enzymes primarily responsible for the oxidative metabolism of sofpironium are CYP2D6 and CYP3A4. Nonclinical metabolism studies showed that the major *in vivo* and *in vitro* sofpironium metabolite is BBI-4010; it is the only metabolite that exceeded greater than 10% of total drug exposure in plasma and/or urine of rats, minipigs, and humans.

Sofpironium is an inhibitor of CYP2D6, CYP3A4, OCT1, OCT2, and MATE1 in vitro. Sofpironium is not an inducer of CYP1A2, CYP2B6, or CYP3A4. No clinically significant differences in sofpironium pharmacokinetics were observed when used concomitantly with inhibitors of,

CYP3A4(itraconazole), and inhibitor of OCT2, MATE1, or MATE2-K (Cimetidine) in a clinical DDI study.

In presence of 20 mg oral dose of paroxetine HCL (strong CYP2D6 inhibitor) C_{max} and AUC_{0-t} of sofpironium increased by approximately 2-fold compared to when sofpironium bromide topical gel, 15%, was administered alone.

The results from a thorough QT/corrected QT interval (QTc) study (Study BBI-4000-CL-106) showed that at a dose 6 times the maximum approved recommended dose, leading to an exposure 3 times the exposure associated with the maximum approved recommended dose, sofpironium does not prolong the QTc interval to any clinically relevant extent.

No apparent dose-response in efficacy was observed when the efficacy of various strengths of sofpironium bromide gel (5%, 10%, and 15%) was evaluated in Phase 2 study (Study BBI-4000-CL-203). The results of the study indicated that topically applied sofpironium bromide gel, at all strengths tested, improved multiple efficacy outcomes, and reduced hyperhidrosis disease severity in subjects with axillary hyperhidrosis. In addition, topically applied sofpironium bromide gel, 15% and 5%, showed improvements in gravimetric sweat production (GSP), with the greatest improvements observed with the 15% gel. Based on these results, 15% concentration was selected as the dose to be further evaluated in the phase 3 studies.

The efficacy of the 15% concentration was assessed and confirmed in the two pivotal Phase 3 trials (Study BBI-4000-CL-301 and Study BBI-4000-CL-302), with both trials meeting both co-primary endpoints and all three secondary endpoints. Persistence of efficacy of sofpironium bromide gel, 15% was explored in subjects ≥9 years of age with primary axillary hyperhidrosis in two open-label studies, Phase 3 Study BBI-4000-CL-303 (subjects ≥9 years of age) and Phase 1 Study BBI-4000-CL-108 (subjects ≥9 years to <17 years of age previously enrolled in Study BBI-4000-CL-105). Overall, sofpironium bromide gel, 15% was found to have a persistent treatment effect without tolerance to the effect for up to 48 weeks and 26 weeks in Study BBI-4000-CL-303 and Study BBI-4000-CL-108, respectively, with evidence of treatment effect remaining 4 weeks and 2 weeks post-treatment. Please refer to the section 7 and 8 for more details on efficacy and safety.

Overall, the results of the two phase 3 clinical trials, BBI-4000-CL-301 and BBI-4000-CL-302, demonstrated that sofpironium bromide gel, 15%, at the proposed dose of applying 1 pump of sofpironium bromide gel, 15% (sofpironium base 12.45%) per underarm once a day at bedtime, was efficacious in the treatment of patients with primary axillary hyperhidrosis.

Recommendations

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under NDA 217347 and finds the NDA approvable.

Post marketing requirement/Post marketing commitment
None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.0. Pharmacology and Clinical Pharmacokinetics

Absorption

The pharmacokinetics of sofpironium were evaluated in adult patients with primary axillary hyperhidrosis following application of sofpironium bromide gel, 15% once daily to the underarms for 21 days. The mean ± standard deviation (SD) exposures of sofpironium in adults are presented in Table 6.2.1.1. There was no evidence of accumulation on multiple dosing.

Table 6.2.1.1: Mean (SD) Plasma Exposure of Sofpironium in Adults Following Sofpironium Bromide Gel, 15% on Day 1.

PK Parameter	Adult Patients
C_{max} (ng/mL)	2.71 (6.94)
AUC_{0-t} (ng·hr/mL)	45.1 (85.1)
t_{max} (hr)	5.34 (5.45)

Distribution

Plasma protein binding of sofpironium is around 34.8 - 37.8%. The major sofpironium metabolite (BBI-4010) had plasma protein binding around 2.3 - 3.7%.

Elimination

Metabolism
Sofpironium is metabolized by nonenzymatic hydrolysis, CYP2D6 and CYP3A4 mediated-oxidative metabolism, and glycine conjugation. In plasma, sofpironium was the major component (38%) followed by the BBI-4010 (20%) metabolite.

Excretion
Urinary excretion of sofpironium and BBI-4010 were less than 0.5% of the applied dose.

Specific Populations
The pharmacokinetics of sofpironium were not evaluated in pregnant women or patients with hepatic or renal impairment. No clinical studies were conducted in these patient population.

Pediatric Subjects

The mean ± SD exposures of sofpironium after a single dose in pediatric subjects 9 years to 16 years of age are presented in Table 6.2.1.2. After 24 weeks of dosing, trough concentrations of sofpironium were slightly lower than adults and there was no evidence of accumulation on multiple dosing. The exposure to major metabolite (BBI-4010) in pediatric subjects was similar to sofpironium exposure in adults.

Table 6.2.1.2: Mean (SD) Plasma Exposure of Sofpironium in Pediatric Subjects Following Single Dose Administration of Sofpironium Bromide Gel, 15% on Day 1.

PK Parameter	Pediatric Patients
C_{max} (ng/mL)	1.30 (3.16)
AUC_{0-t} (ng·hr/mL)	14.6 (35.0)
t_{max} (hr)	4.0 (0.9, 23.1)

Note: t_{max} reported as median and range.

Drug Interaction Studies

No clinically significant differences in sofpironium pharmacokinetics were observed when used concomitantly with inhibitors of, CYP3A4, OCT2, MATE1, or MATE2-K.

In vivo Study

In presence of 20 mg oral dose of paroxetine HCL (strong CYP2D6 inhibitor) C_{max} and AUC_{0-t} of sofpironium increased by approximately 2 fold compared to when sofpironium bromide topical gel, 15%, was administered alone.

In vitro Studies

Sofpironium is an inhibitor of CYP2D6, CYP3A4, OCT1, OCT2, and MATE1 in vitro. Sofpironium is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The proposed maximum therapeutic dose is to apply 1 pump of sofpironium bromide gel, 15% (sofpironium topical gel, 12.45%) per underarm once a day at bedtime.

Therapeutic Individualization

Not Applicable.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Review Issues	Recommendations and Comments
Mechanism of Action	Sofpironium bromide is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. Sofpironium bromide indirectly reduces the rate of sweating by preventing the stimulation of these receptors.
QT Prolongation	At an exposure 3 times the exposure associated with the maximum approved recommended dose, sofpironium does not prolong the QTc interval to any clinically relevant extent.
General Information	
Bioanalysis	Sofpironium, and BBI-4010 plasma and urine concentrations were measured using validated high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS).
Healthy Volunteers vs. Patients	In the population PK Report, the exposure to sofpironium was found to be similar for healthy subjects and those with hyperhidrosis. Across the clinical program, and regardless of whether the subject was healthy or had hyperhidrosis, systemic exposure of sofpironium and BBI-4010 was typically low following the first dose and accumulation was not observed on multiple dosing.
Drug exposure at steady state following the therapeutic dosing regimen	Steady state appeared to be reached within the first 24 hours, but this could not be firmly established owing to the low systemic exposure of sofpironium and BBI-4010, as most samples analyzed were below 1 ng/mL or below the lower limit of quantification (0.05 ng/mL).
Maximal tolerated dose or exposure	A single dose that was 6-fold higher than the proposed therapeutic dose (applied to the axillae, lateral side of the upper arms, ventral side of the thighs, and central abdomen under occlusion; 1038 mg of sofpironium bromide) was well tolerated in healthy adult subjects, despite a 2- to 4-fold increase in exposure (Studies BBI-4000-CL-106)
Dose Proportionality	Systemic exposure to sofpironium appeared to increase in an approximately dose-proportional manner between the 5% and 15% gel concentrations, indicating that applying a more concentrated gel increased exposure (between 2- and 10-fold) (Study BBI-4000-CL-103 and Study BBI-4000-03). However, inter-subject variability of PK parameters was extremely high, hence concrete conclusions on dose proportionality cannot be made.
Accumulation	Across the program, systemic exposure of sofpironium and BBI-4010 was typically low following the first dose (Day 1) and subsequent PK assessment visits, and accumulation was not

	observed on multiple dosing.
Absorption	
t_{max}	Maximum plasma concentrations of BBI-4000 generally occurred at a median t_{max} of 4 hours post-dose on Days 1 and 21. (Study BBI-4000-CL-102)
Food effect	Food effect was not evaluated in this NDA.
Distribution	
Plasma protein binding	Plasma protein binding of sofpironium is around 34.8 - 37.8%. The major sofpironium metabolite (BBI-4010) had plasma protein binding around 2.3 - 3.7%.
Elimination	
Mean Terminal Elimination half-life	The half-life of sofpironium in MUPK study BBI-4000-CL-102, was around 4 to 6 hrs, however in most of the PK studies it was not possible to reliably estimate due to the scarcity and variability of the data.
Metabolism	
Primary metabolic pathway(s) [in-vivo]	No clinically significant differences in sofpironium pharmacokinetics were observed when used concomitantly with inhibitors of, CYP3A4, OCT2, MATE1, or MATE2-K.
[*in-vivo*]	In presence of 20 mg oral dose of paroxetine HCL (strong CYP2D6 inhibitor) C_{max} and AUC_{0-t} of sofpironium increased by approximately 2 fold compared to when sofpironium bromide topical gel, 15%, was administered alone.
Inhibitor/Inducer [in-vitro]	Sofpironium is an inhibitor of CYP2D6, CYP3A4, OCT1, OCT2, and MATE1 in vitro. Sofpironium is not an inducer of CYP1A2, CYP2B6, or CYP3A4.
Excretion	
Primary excretion pathway	Urinary excretion of sofpironium and BBI-4010 were less than 0.5% of the applied dose.

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed maximum therapeutic dose is once daily topical administration of sofpironium APPEARS THIS WAY ON ORIGINAL
bromide gel, 15% (1 actuation per axilla) (12.45% free base).

Systemic exposure to sofpironium appeared to increase in an approximately dose-proportional manner between the 5% and 15% gel concentrations, indicating that applying a more concentrated gel produced increased exposure (Study BBI-4000-CL-103 and Study BBI-4000-03). It is noted that the inter-subject variability of PK parameters was extremely high (between 2- and 10-fold; Studies BBI-4000-CL-103 and BBI-4000-03) and hence concrete conclusions on dose proportionality cannot be made. Across the program, and regardless of whether the

subject was healthy or had hyperhidrosis, the systemic exposure of sofpironium and BBI-4010 was typically low following the first dose (Day 1) and at subsequent PK assessment visits, and accumulation was not observed.

The efficacy of various strengths of sofpironium bromide gel (5%, 10%, and 15%) was evaluated in Study BBI-4000-CL-203; a randomized, double-blinded, vehicle-controlled study. The results of this trial indicated that topically applied sofpironium bromide gel, at all strengths tested, improved multiple efficacy outcomes (HDSM-Ax-11, HDSS, and GSP) and reduced hyperhidrosis disease severity in subjects with axillary hyperhidrosis. For the primary efficacy continuous endpoint, the differences in the mean change from baseline to end of therapy between 15% and vehicle (least square mean difference [LSMD, 15%-vehicle] = -0.80), between 10% and vehicle (LSMD [10%-vehicle] = -0.78), and between 5% and vehicle (LSMD [5%-vehicle] = -0.72). In addition, topically applied sofpironium bromide gel, 15% and 5%, showed improvements in gravimetric sweat production (GSP), with the greatest improvements observed with the 15% gel. No dose response was observed for the assessment of HDSM-Ax-11, but a trend for better improvement in GSP response was observed with higher concentrations of sofpironium bromide, thus supporting the selection of the 15% gel for further development.

The efficacy of the 15% concentration was assessed and confirmed in the two pivotal Phase 3 trials (Study BBI-4000-CL-301 and Study BBI-4000-CL-302), with both studies meeting both co-primary endpoints and all three secondary endpoints. An acceptable benefit-risk profile was also observed. Please refer to the section 7 and 8 for more details on efficacy and safety.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. As this is a topical product, most of the intrinsic and extrinsic factors were generally not applicable as systemic concentrations were generally low. Some of the special populations are explained as below.

Pediatric

The pharmacokinetic properties of sofpironium bromide gel, 15% have been evaluated in two studies in pediatric subjects ≥9 to <17 years of age with primary axillary hyperhidrosis and were treated for up to 24 weeks. Subjects aged 9 years and older have also been included in the Phase 3 pivotal studies.

In the pediatric subjects exposed to sofpironium bromide gel to date, PK, safety, and local tolerability outcomes were consistent with the findings noted in adult subjects. After the initial dose, the geometric mean Cmax value for both sofpironium and BBI-4010 was 1.0 ng/mL. The geometric mean $AUC_{0\text{-last}}$ on Day 2 (24 hours after the first dose and before the second dose) was 2.0 ng*hr/mL for sofpironium and 1.5 ng*hr/mL for BBI-4010. The median tmax was 4.0 hours (range 0.9 to 23 hours) for sofpironium and 8.0 hours for BBI-4010. The mean time to last measurable concentration was 8.0 hours (range 1.0 to 25.0 hours) for sofpironium and 23.1

hours (range 7.8 to 24.9) for BBI-4010. The t½ was could not be reliably estimated due to the scarcity and variability of the data.

The evaluation of adverse events (AEs), routine laboratory assessments, physical examinations, electrocardiograms (ECGs), application site tolerability assessments, and vital signs (blood pressure and heart rate) revealed no safety concerns for use in pediatric subjects aged ≥9 to <17 years. No studies have been conducted to evaluate the safety of sofpironium bromide gel in pediatric populations <9 years of age. Sofpironium bromide gel should not be used in subjects <9 years of age.

This reviewer notes that, there is very limited data available from lower age group and the median age was around 14.0 years (range of 9 to 16 years). Among 25 pediatric subjects there were 7 subjects in 9 to ≤12 years age group and 18 subjects (12 to ≤17 years). Systemic exposure to topically applied sofpironium was detected only in 11 subjects (including 2 subjects in 9 to ≤12 years age range). Overall high variability was observed in the PK data.

Table 6.3.2.1 Demographics Characteristics for Pediatric (BBI-4000-CL-105) and Adult Subjects (BBI-4000-CL-102) with Axillary Hyperhidrosis.

	BBI-4000-CL-105 Pediatric Study (N=25)	BBI-4000-CL-102 MUPK Study in Adults (Cohort A) (N=12)
Population	Children and adolescents, ≥9 to <17 years of age, with axillary hyperhidrosis	Adult subjects with axillary hyperhidrosis
Age (years)		
n	25	12
Mean (SD)	13.4 (2.14)	27(7)
Median	14.0	26
Min, Max	9, 16	18,45
Gender		
Male	12 (48.0%)	3 (25.0%)
Female	13 (52.0%)	9 (75.0%)
Race		
American Indian or Alaska Native	0	
Asian	0	
Black or African American	2 (8.0%)	4 (33.3%)
Native Hawaiian or Other Pacific Islander	0	
White	22 (88.0%)	8 (66.7%)
Multiple[a]	1 (4.0%)	
Weight (cm)		
n	25	12
Mean (SD)	59.26 (20.313)	67.52 (12.224)

Median	56.00	64.20
Min, Max	30.9, 130.6	55.00,94.60

Abbreviations: Max = maximum; Min = minimum; n = number of subjects in category; N = number of subjects in population; SD = standard deviation,
Note: Cohort A = 15% BBI-4000 IPM gel applied to the diseased skin (axillae)
a Subject 103-006 marked Asian and White races

(Source: Clinical Study Report BBI-4000-CL-105, Table 10-2, Page 45, and Clinical Study Report BBI-4000-CL-102, Table 10-2, Page 32)

Renal Impairment

No clinical studies were conducted to assess the PK of sofopirnium bromide 15% in patients with renal impairment.

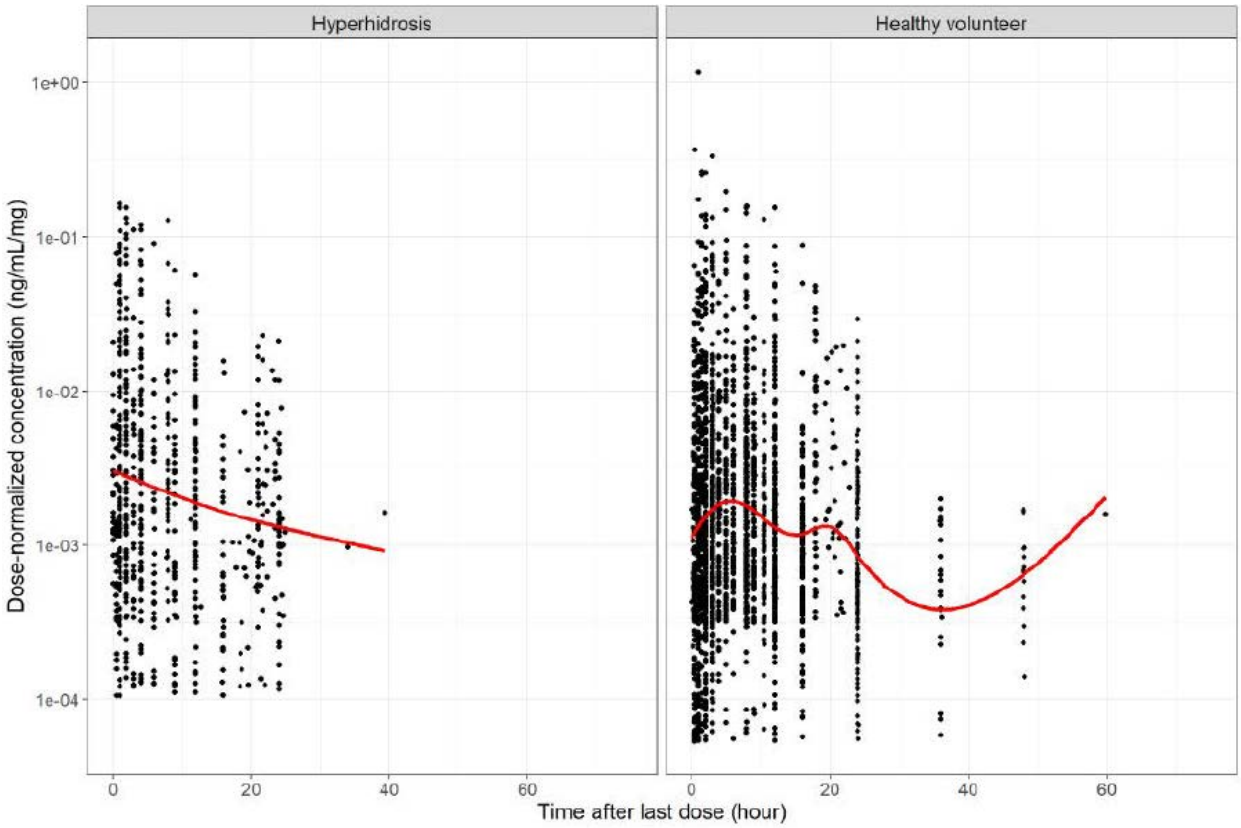
Hepatic Impairment

No clinical studies were conducted to assess the PK of sofopirnium bromide 15% in patients with hepatic impairment.

Does disease severity have any impact on the sofpironium (BBI-4000) PK exposures?

Across the clinical program, and regardless of whether the subject was healthy or had hyperhidrosis, systemic exposure of sofpironium and BBI-4010 was typically low following the first dose and accumulation was not observed on multiple dosing. Inter-subject variability in PK parameters was high. Although the BBI-4010 metabolite was not assessed, in the Population PK Report exposure to sofpironium was found to be similar for healthy subjects and in subjects with hyperhidrosis.

Figure 6.3.2.1: Dose Normalized Sofpironium Concentration Versus TAD by Disease Status (Up to 75 Hours)



TAD = time since last dose
(Source: Response to Clinical Pharmacology Information Request, dated March 29,2023)

This reviewer notes that there were different combinations of entry criteria for some clinical studies in subjects with axillary hyperhidrosis, but only the maximal-use PK (MUPK) study (Study BBI-4000-CL-102) and a pediatric study (Study BBI-4000-CL-105) used the hyperhidrosis disease severity measure - axillary (HDSM-Ax) as a criterion for enrollment. Therefore, grouping subjects with axillary hyperhidrosis by disease severity in all studies is not possible. In both studies with regards to disease severity, since not all subjects have AUC and Cmax parameters for comparison, further subdividing the disease population will result in boxes with a very small number of subjects, which could create an apparent skew in the data. Therefore, a comparison of the PK across studies is presented for sofpironium and the metabolite BBI-4010 in Table 6.3.2.2 and Table 6.3.2.3, respectively. Although PK was quite variable, there is no discernable pattern demonstrating a difference in exposure in healthy subjects versus in subjects with hyperhidrosis. A substantial number of clinical plasma samples were BLQ for both sofpironium and BBI-4010. Because of this, PK parameters were not calculable in all subjects receiving sofpironium bromide. Across studies, different sampling schemes were also used to quantitate sofpironium and BBI-4010, such that AUC values were not always comparable across studies. Therefore, given that many subjects did not have quantifiable concentrations over the sampling

period, and AUC estimates may not be comparable between studies, box plots of PK parameters for sofpironium and BBI-4010 do not provide a useful comparison of subjects.

Table 6.3.2.2: Comparative Arithmetic Mean Pharmacokinetics of Sofpironium after Administration of Sofpironium Bromide Gel

Study	Treatment Group	C_{max} (ng/mL) Mean (SD)				AUC_{0-t} (ng*hr/mL) Mean (SD)			
		Day 1	Day 14	Day 21	Day 28	Day 1	Day 14	Day 21	Day 28
Adult Studies in Healthy Subjects									
BBI-4000-CL-103 (bridging study) [1]	5% Gel (N=10)	NC	1.73 (1.50)	NA	NA	NC	28.7 (24.7)	NA	NA
	15% Gel (N=10)	0.479 (0.409)	5.32 (6.10)	NA	NA	7.03 (6.39)	82.8 (84.3)	NA	NA
BBI-4000-CL-109 (occlusion) [2]	15% Gel (normal use) (N=12)	0.13 (0.02)	NA	NA	NA	1.25 (1.09)	NA	NA	NA
	15% Gel (maximum use) (N=12)	0.21 (0.09)	NA	NA	NA	2.80 (0.93)	NA	NA	NA
	15% Gel (occlusion) (N=12)	1.28 (1.30)	NA	NA	NA	27.00 (27.17)	NA	NA	NA
BBI-4000-CL-106 (QT/QTc) [3]	15% Gel (normal use) (N=60)	0.54 (0.83)	NA	NA	NA	7.95 (13.67)	NA	NA	NA
	15% Gel (occlusion) (N=60)	0.92 (0.93)	NA	NA	NA	11.03 (10.72)	NA	NA	NA
BBI-4000-CL-104 (DDI) [4]	15% Gel (N=24); Treatment A	0.15 (0.06)	NA	NA	NA	1.51 (0.84)	NA	NA	NA
	15% Gel after 11 days of paroxetine HCl (fasted); Treatment B	0.24 (0.20)	NA	NA	NA	3.19 (3.78)	NA	NA	NA
	15% Gel (N=24); Treatment C	0.76 (0.67)	NA	NA	NA	9.48 (10.33)	NA	NA	NA
	15% Gel after 5 days of cimetidine (fasted); Treatment D	0.29 (0.13)	NA	NA	NA	6.01 (5.52)	NA	NA	NA
	15% Gel after 7 days of itraconazole (fed); Treatment E	0.32 (NR)	NA	NA	NA	8.98 (NR)	NA	NA	NA
Adult Studies in Hyperhidrosis Subjects									
BBI-4000-CL-102 (maximum use) [5]	15% Gel (normal use) (N=12)	1.18 (2.06)	NA	0.609 (0.723)	NA	24.2 (36.5)	NA	14.1 (13.0)	NA
	15% Gel (maximum use) (N=18)	0.674 (0.690)	NA	0.286 (0.278)	NA	11.1 (10.7)	NA	5.41 (5.99)	NA
BBI-4000-03 (repeat dose) [6]	5% Gel (N=6)	0.0462 (0.113)	0.464 (0.736)	NA	0.184 (0.411)	0.575 (1.41)	7.21 (11.9)	NA	2.62 (5.35)
	15% Gel (N=6)	0.388 (0.597)	1.25 (1.78)	NA	4.30 (4.74)	5.98 (8.69)	17.2 (24.5)	NA	40.2 (45.0)
BBI-4000-05 (bridging study) [7]	15% Gel (N=12)	NA	0.01 (0.05)	NA	NA	NA	0.17 (0.57)	NA	NA
Pediatric Study in Hyperhidrosis Subjects									
BBI-4000-CL-105 (pediatric) [8]	15% Gel (normal use) (N=25)	0.33 (0.94)	NA	NA	NA	4.94 (15.03)	NA	NA	NA

NA = Data not collected as part of study; NC = not calculated

[1] BBI-4000-CL-103 Day 1: 5% gel (N = 10 dosed; N = 9 completed study), Cmax (N = 5) and AUC0-t (N = 3); 15% gel (N = 10 dosed; N = 10 completed study) Cmax (N = 8) and AUCo-t (N = 8). Day 14: 5% gel Cmax (N = 8) and AUCo-t (N = 8); 15% gel Cmax (N = 10) and AUCo-t (N = 10).
[2] Overall in BBI-4000-CL-109, N =12 subjects dosed and all subjects completed. Normal use: Cmax (N = 5) and AUCo-t (N = 5). Maximal use, unoccluded: Cmax (N = 8) and AUCo-t (N = 8); Cmax includes a major outlier, with a concentration of 164 ng/mL (Subject (b) (6)), which affected both Cmax and AUC0-t parameters. Maximal use, occuluded: Cmax (N = 11) and AUCo-t (N = 11).
[3] Overall in BBI-4000-CL-109, N = 60 subjects dosed and 58 subjects completed. Normal use: Cmax (N = 35) and AUCo-t (N = 35); Occlusion: Cmax (N = 60) and AUCo-t (N = 50)
[4] Overall in BBI-4000-CL-104, N = 48 enrolled and completed, 24 subjects in Part 1 (Treatment A and B) and Part 2 (Treatments C, D, and E). Treatment A: 1.34 mL sofpironium bromide el, 15% on Day 1; Cmax (N = 11) and AUCo-t (N = 11). Treatment B: 20 mg paroxetine HCl QD for 12 consecutive days (Days 1-12) (Fasted) coadministered with 1.34 mL sofpironium bromide gel, 15% on Day 11 ; Cmax (N = 17) and AUCo-t (N = 17). Treatment C: 1.34 mL sofpironium bromide gel, 15% on Day 1; Cmax (N = 9) and AUCo-t (N = 9). Treatment D: 800 mg cimetidine BID for 5 days (Days 1-5) (Fasted) coadministered with 1.34 mL sofpironium bromide gel, 15% on Day 4; Cmax (N = 6) and AUCo-t (N = 6). Treatment E: 200 mg itraconazole QD for 7 days (Days 1-7) (Fed) coadministered with 1.34 mL sofpironium bromide gel, 15% on Day 6; Cmax (N = 10) and AUCo-t (N = 10)
[5] In Study BBI-4000-CL-102, 18 subjects were dosed; 16 subjects completed the study. Normal use: Day 1 Cmax (N = 9) and AUCo-t (N = 5) ; Day 21 Cmax (N = 7) and AUCo-t (N = 6). Maximum use: Day 1 Cmax (N = 16) and AUCo-t (N = 11) ; Day 21 Cmax (N = 14) and AUCo-t (N = 10).
[6] In Study BBI-4000-03, 6 subjects were enrolled in each group and all but one subject completed the study (in the 5% gel group). For the 5% gel, Day 1 Cmax (N = 6) and AUCo-t (N = 6); Day 14 Cmax (N = 6) and AUCo-t (N = 6); Day 21 Cmax (N = 5 and AUCo-t (N = 5). For the 15% gel, Day 1 Cmax (N = 6) and AUCo-t (N = 6); Day 14 Cmax (N = 6) and AUCo-t (N = 6); Day 21 Cmax (N = 6) and AUCo-t (N = 6).
[7] In Study BBI-4000-05 (12 enrolled in the intended commercial 15% gel arm, 11 completed) Day 14 Cmax (N = 4) and AUCo-t (N = 4).
[8] Minimal samples were collected in Study BBI-4000-CL-105 (predose, and 1, 4, 8, and 24 hours postdose). Twenty-five subjects were enrolled. Day 1 Cmax (N = 11) and AUCo-t (N = 11).

(Source: Response to Clinical Pharmacology Information Request, dated March 29,2023)

Table 6.3.2.3: Comparative Arithmetic Mean Pharmacokinetics of BBI-4010 after Administration of Sofpironium Bromide Gel.

Study	Treatment Group	C_{max} (ng/mL) Mean (SD)				AUC_{0-t} (ng*hr/mL) Mean (SD)			
		Day 1	Day 14	Day 21	Day 28	Day 1	Day 14	Day 21	Day 28
Adult Studies in Healthy Subjects									
BBI-4000-CL-103 (bridging study) [1]	5% Gel (N=10)	NC	1.73 (1.50)	NA	NA	NC	28.7 (24.7)	NA	NA
	15% Gel (N=10)	0.479 (0.409)	5.32 (6.10)	NA	NA	7.03 (6.39)	82.8 (84.3)	NA	NA
BBI-4000-CL-109 (occlusion) [2]	15% Gel (normal use) (N=12)	0.13 (0.02)	NA	NA	NA	1.25 (1.09)	NA	NA	NA
	15% Gel (maximum use) (N=12)	0.21 (0.09)	NA	NA	NA	2.80 (0.93)	NA	NA	NA
	15% Gel (occlusion) (N=12)	1.28 (1.30)	NA	NA	NA	27.00 (27.17)	NA	NA	NA
BBI-4000-CL-106 (QT/QTc) [3]	15% Gel (normal use) (N=60)	0.54 (0.83)	NA	NA	NA	7.95 (13.67)	NA	NA	NA
	15% Gel (occlusion) (N=60)	0.92 (0.93)	NA	NA	NA	11.03 (10.72)	NA	NA	NA
BBI-4000-CL-104 (DDI) [4]	15% Gel (N=24); Treatment A	0.15 (0.06)	NA	NA	NA	1.51 (0.84)	NA	NA	NA
	15% Gel after 11 days of paroxetine HCl (fasted); Treatment B	0.24 (0.20)	NA	NA	NA	3.19 (3.78)	NA	NA	NA
	15% Gel (N=24); Treatment C	0.76 (0.67)	NA	NA	NA	9.48 (10.33)	NA	NA	NA
	15% Gel after 5 days of cimetidine (fasted); Treatment D	0.29 (0.13)	NA	NA	NA	6.01 (5.52)	NA	NA	NA

Study	Treatment Group	C_{max} (ng/mL) Mean (SD)				AUC_{0-t} (ng*hr/mL) Mean (SD)			
		Day 1	Day 14	Day 21	Day 28	Day 1	Day 14	Day 21	Day 28
	15% Gel after 7 days of itraconazole (fed); Treatment E	0.32 (NR)	NA	NA	NA	8.98 (NR)	NA	NA	NA
Adult Studies in Hyperhidrosis Subjects									
BBI-4000-CL-102 (maximum use) [5]	15% Gel (normal use) (N=12)	1.18 (2.06)	NA	0.609 (0.723)	NA	24.2 (36.5)	NA	14.1 (13.0)	NA
	15% Gel (maximum use) (N=18)	0.674 (0.690)	NA	0.286 (0.278)	NA	11.1 (10.7)	NA	5.41 (5.99)	NA
BBI-4000-03 (repeat dose) [6]	5% Gel (N=6)	0.0462 (0.113)	0.464 (0.736)	NA	0.184 (0.411)	0.575 (1.41)	7.21 (11.9)	NA	2.62 (5.35)
	15% Gel (N=6)	0.388 (0.597)	1.25 (1.78)	NA	4.30 (4.74)	5.98 (8.69)	17.2 (24.5)	NA	40.2 (45.0)
BBI-4000-05 (bridging study) [7]	15% Gel (N=12)	NA	0.01 (0.05)	NA	NA	NA	0.17 (0.57)	NA	NA
Pediatric Study in Hyperhidrosis Subjects									
BBI-4000-CL-105 (pediatric) [8]	15% Gel (normal use) (N=25)	0.33 (0.94)	NA	NA	NA	4.94 (15.03)	NA	NA	NA

NA = Data not collected as part of study; NC = not calculated
[1] BBI-4000-CL-103 Day 1: 5% gel (N = 10 dosed; N = 9 completed study), Cmax (N = 2) and AUC0-t (N = 1); 15% gel (N = 10 dosed; N = 10 completed study) Cmax (N = 3) and AUCo-t (N = 3). Day 14: 5% gel Cmax (N = 5) and AUCo-t (N = 5); 15% gel Cmax (N = 8) and AUCo-t (N = 8).
[2] Overall in BBI-4000-CL-109, N =12 subjects dosed and all subjects completed. Normal use: Cmax (N = 3) and AUCo-t (N = 3). Maximal use, unoccluded: Cmax (N = 4) and AUCo-t (N = 4). Maximal use, occuluded: Cmax (N = 10) and AUCo-t (N = 10).
[3] Overall in BBI-4000-CL-109, N = 60 subjects dosed and 58 subjects completed. Normal use: Cmax (N = 19) and AUCo-t (N = 19); Occlusion: Cmax (N = 58) and AUCo-t (N = 58).
[4] Overall in BBI-4000-CL-104, N = 48 enrolled and completed, 24 subjects in Part 1 (Treatment A and B) and Part 2 (Treatments C, D, and E). Treatment A: 1.34 mL sofpironium bromide el, 15% on Day 1; Cmax (N = 3) and AUCo-t (N = 3). Treatment B: 20 mg paroxetine HCl QD for 12 consecutive days (Days 1-12) (Fasted) coadministered with 1.34 mL sofpironium bromide gel, 15% on Day 11 ; Cmax (N = 10) and AUCo-t (N = 10). Treatment C: 1.34 mL sofpironium bromide gel, 15% on Day 1; Cmax (N = 6) and AUCo-t (N = 6). Treatment D: 800 mg cimetidine BID for 5 days (Days 1-5) (Fasted) coadministered with 1.34 mL sofpironium bromide gel, 15% on Day 4; Cmax (N = 3) and AUCo-t (N = 3). Treatment E: 200 mg itraconazole QD for 7 days (Days 1-7) (Fed) coadministered with 1.34 mL sofpironium bromide gel, 15% on Day 6; Cmax (N = 1) and AUCo-t (N = 1)
[5] In Study BBI-4000-CL-102, 18 subjects were dosed; 16 subjects completed the study. Normal use: Day 1 Cmax (N = 4) and AUCo-t (N = 3); Day 21 Cmax (N = 5) and AUCo-t (N = 3). Maximum use: Day 1 Cmax (N = 9) and AUCo-t (N = 8) ; Day 21 Cmax (N = 8) and AUCo-t (N = 7).
[6] In Study BBI-4000-03, 6 subjects were enrolled in each group and all but one subject completed the study (in the 5% gel group). For the 5% gel, Day 1 Cmax (N = 1) and AUCo-t (N = 1); Day 14 Cmax (N = 4) and AUCo-t (N = 4); Day 28 Cmax (N = 1 and AUCo-t (N = 1). For the 15% gel, Day 1 Cmax (N = 3) and AUCo-t (N = 3); Day 14 Cmax (N = 6) and AUCo-t (N = 6); Day 21 Cmax (N = 6) and AUCo-t (N = 6).
[7] In Study BBI-4000-05 (12 enrolled in the intended commercial 15% gel arm, 11 completed) Day 14 Cmax (N = 1) and AUCo-t (N = 1).
[8] Minimal samples were collected in Study BBI-4000-CL-105 (predose, and 1, 4, 8, and 24 hours postdose). Twenty-five subjects were enrolled. Day 1 Cmax (N = 5) and AUCo-t (N = 5).

(Source: Response to Clinical Pharmacology Information Request, dated March 29,2023)

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions

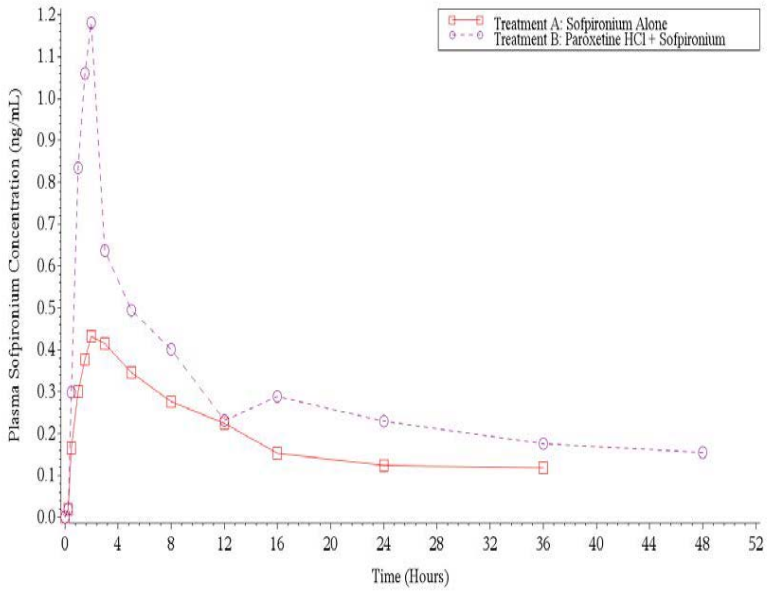
Food -drug interactions are not applicable for topical products.

Drug-drug interactions

In general, no clinically significant differences in sofpironium pharmacokinetics were observed when used concomitantly with inhibitors of, CYP3A4, OCT2, MATE1, or MATE2-K. Sofpironium is an inhibitor of CYP2D6, CYP3A4, OCT1, OCT2, and MATE1 in vitro. Sofpironium is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

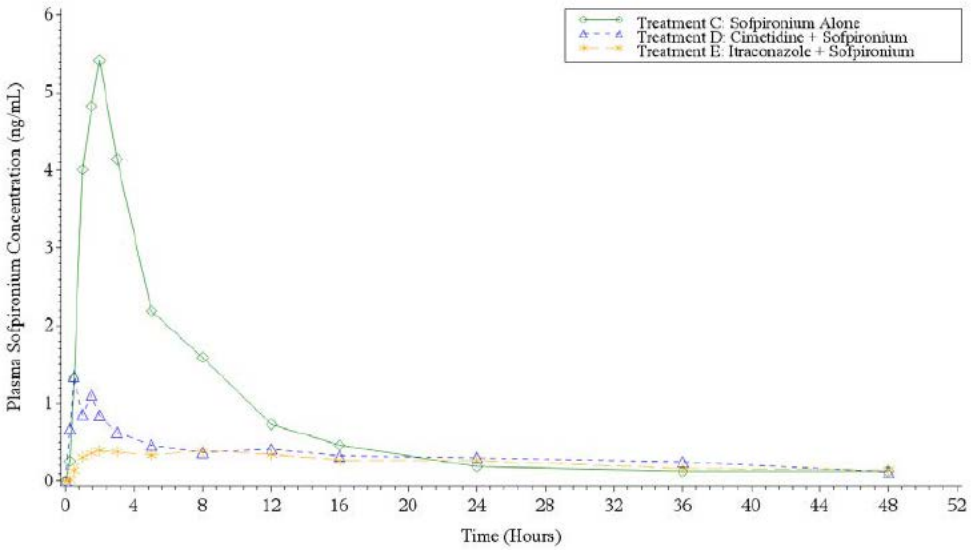
A clinical DDI study (Study BBI-4000-CL-104) was conducted to determine the effect of oral doses of paroxetine HCl (CYP2D6 inhibitor), cimetidine (an OCT2/ MATE1/MATE2-K inhibitor), and itraconazole (a CYP3A4 inhibitor) on sofpironium PK after a single topical application in healthy adult subjects. Administration of oral paroxetine HCl with sofpironium bromide gel, 15%, produced an increase in the peak sofpironium systemic exposure by 112% and increased total sofpironium systemic exposure by 136% (Figure 6.3.2.2 below). Administration of oral cimetidine with sofpironium bromide gel, 15%, reduced peak sofpironium systemic exposure by 59%, reduced total sofpironium systemic exposure by 37%, and increased clearance (CLr) of sofpironium by 35%. Administration of oral itraconazole with sofpironium bromide gel, 15% reduced peak sofpironium systemic exposure by 91% and reduced total sofpironium systemic exposure by 83% to 87%.

Figure 6.3.2.2 Arithmetic Mean Plasma Sofpironium Concentrations-time Profiles Following Administration of 1.34 mL Sofpironium Bromide Gel, 15% Coadministered with 20 mg Paroxetine HCl Versus Administration of Sofpironium Bromide Gel, 15% Alone (Part 1) (Linear Scale)



(Source: Summary of Clinical Pharmacology Figure 10, Page 43.)

Figure 6.3.2.3 Arithmetic Mean Plasma Sofpironium Concentrations-Time Profiles Following Administration of 1.34 mL Sofpironium Bromide Gel, 15% Coadministered with 800 mg Cimetidine, 200 mg Itraconazole, and Alone (Part 2) (Linear Scale)



(Source: Summary of Clinical Pharmacology Figure 11, Page 45.)

There was an approximate 2-fold increase in systemic exposure when sofpironium was co-administered with 20 mg of paroxetine HCl versus sofpironium alone. However, (b) (4) in anticholinergic AEs, such as dry mouth, blurred vision, urinary hesitation, or constipation, observed with marginally higher absolute measurements of systemic exposure.

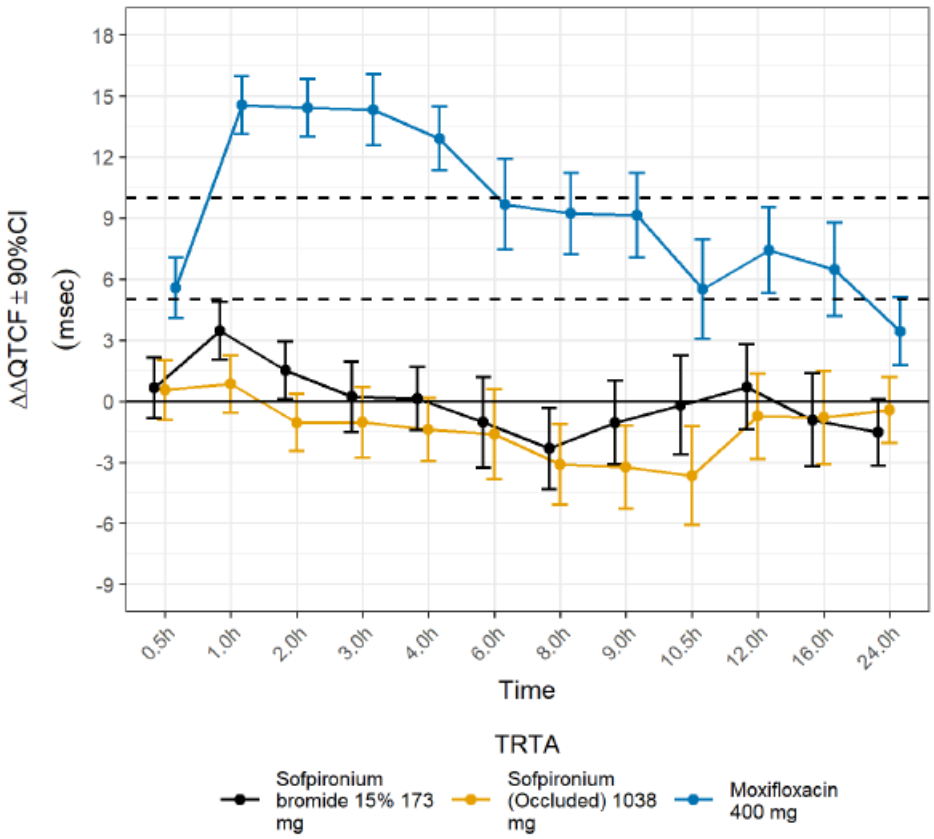
After careful consideration, the review team agreed to add a following precaution in the labeling language that " (b) (4) with drugs that are strong inhibitors of CYP2D6".

Does sofpironium (BBI-4000) shows any clinically relevant prolongation of the corrected QT interval (QTc) in healthy subjects?

No. Sofpironium bromide did not prolong the QTcF interval in this Thorough QT study (BBI-4000-CL-106) which was a four-way, crossover, randomized, double-blind, placebo- and active-controlled study to evaluate the effect of a single therapeutic or supratherapeutic dose of sofpironium bromide gel (15%), applied topically, on the QTc intervals in adult healthy subjects (n=60). The highest dose provided 3.2-fold high clinical exposure. Data were analyzed using by-time analysis as the primary analysis, which did not suggest that Sofpironium bromide is

associated with significant QTc prolonging effect (refer to section 4.3). The findings of the primary analysis are further supported by the lack of QTc prolongation in nonclinical data, lack of a relationship between concentrations and ΔΔQTc (Figure 6.3.2.4) and no outliers in categorical analysis.

Figure 6.3.2.4: Placebo-Adjusted Mean Change from Baseline-QTcF Interval **(ΔΔQTcF)** Across Time Points.



(Source: QT-IRT FDA reviewer's memo and Summary of Clinical Pharmacology Studies, Figure 6, Page 37)

Are the Bioanalytical Methods Properly Validated to Measure PK in Plasma & Urine Samples?

Well validated bioanalytical methods were developed to quantify sofpironium (BBI-4000) and its metabolite BBI-4010 in plasma and urine. In clinical studies, an aliquot of the extract was injected onto an HPLC/MS/MS triple quadrupole mass spectrometer. A C18 HPLC column was used to separate BBI-4000 and BBI-4010 and their respective internal standard (IS), D9-SGE and D9-SGA, from interfering compounds that may be present in the sample extract. The peak area

of the product ion of the compounds (BBI-4000 and BBI-4010) were measured against the peak area of the product ion of the internal standards (D9-SGE for BBI-4000 and D9-SGA for BBI-4010). A sensitive and specific HPLC-MS assay was also developed for determination of sofpironium (BBI-4000) and its metabolite BBI-4010 in human urine. The bioanalytical reports describe the assay performance and sample assay results. Incurred Sample Reanalysis (ISR) was not performed for most of the study samples as there were insufficient samples above the LLOQ (0.0500 ng/mL). The additional details of bioanalytical methods are provided in Appendix 16.4.0(section 16.4.0).

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

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Table 14: Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
BBI-4000-CL-301	NCT03836287	Multicenter, randomized, double-blind, Vehicle-controlled, pivotal efficacy and safety study	SB gel, 15%; daily; topical Vehicle gel; daily; topical	co-primary efficacy endpoints: 1. HDSM-Ax-7 scale score (proprietary PRO) 2. change in GSP	Tx: 42 days	350	Adult, Pediatric ≥9 yrs w/ primary axillary hyperhidrosis	39 US sites: 35 sites randomized subjects
BBI-4000-CL-302	NCT03948646	Multicenter, randomized, double-blind, Vehicle-controlled, pivotal efficacy and safety study	SB gel, 15%; daily; topical Vehicle gel; daily; topical	co-primary efficacy endpoints: 1. HDSM-Ax-7 scale score (proprietary PRO) 2. change in GSP	Tx: 42 days	351	Adult, Pediatric ≥9 yrs w/ primary axillary hyperhidrosis	42 US sites; 33 sites randomized subjects
-								
		Studies to Support Safety						
BBI-4000-CL-303	NCT03627468	multicenter, open-label extension	SB gel, 5% and 15%; daily; topical	long-term safety, local tolerability of SB gel, 5% & 15%	Tx: 48 weeks	300: 72 Tx w/ SB 5%; 118 Tx w/ SB 15%	≥9 years w/ axillary hyperhidrosis	30 sites, US

BBI 4000-CL-105		Open label	SB gel, 15% topical application of ~0.67 mL QD	1. Assess systemic exposure of sofpironium and its primary metabolite (BBI-4010); 2.Assess safety profile	7 (±1) days	25	Subjects ≥ 9 to <17 years of age with axillary hyperhidrosis	7 sites, US
BBI 4000-CL-108		Open label, long-term study	SB gel, 15% ~0.67 mL applied topically once daily QD	Safety: Assess long-term safety and tolerability of SB 15% PK: Assess systemic exposure (Ctrough) of SB and primary metabolite (BBI-4010)	Tx period=24 weeks, follow-up visit 2 weeks after last dose	21	Subjects who completed study 105, ≥ 9 to < 17 years with axillary hyperhidrosis	7 sites, US
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
BBI-4000-CL-104		Open-label, 2-part, parallel-cohort study	Part 1 (Cohort A) 1/A: SB gel, 15% applied; topical 2/B: SB gel, 15% applied; topical and 20 mg paroxetine HCl; oral; QD Part 2 (Cohort B) 1/C: SB gel, 15% applied; topical 2/D: SB gel, 15% applied; topical and 800 mg cimetidine; BID; oral 3/E: SB gel, 15%; topical and 200 mg itraconazole; daily;	Part 1: Primary PK endpoints SB AUC0-t, AUC0-inf, and Cmax for study drug administered w/ & w/o paroxetine HCl. Part 2: Primary PK endpoints: SB AUC0-t, AUC0-inf, Ae0-48, and Cmax for study	Part 1 SB: single treatment w/ 2-day washout then Paroxetine HCl: 12 days <u>Part 2</u> SB gel, 15%: single treatment with 7-day washout	48 (24 per part)	Healthy male and female adults	1 Site,

			oral	drug administered with and without cimetidine and sofpironium AUC0-t, AUC0-inf, and Cmax for study drug administered with and without itraconazole.	between Periods 1 and 2 and Periods 2 and 3 Cimetidine: 5 days Itraconazole: 7 days			
BBI-4000-CL-203	NCT03024255	R, DB, vehicle-controlled, parallel-group study	Randomized 1:1:1:1 BBI-4000 gel, 5%, 10%, 15%, vehicle gel Applied topically QD	binary measure: ≥ 1-point improvement, baseline to EOT; continuous measure: HDSM-Ax change scores were compared between each active arm vs placebo group in pairwise fashion	42 days	225	Adults with PAH, Sx >= 6 mo	23 Sites, US

Source: Reviewer table.

7.2. Review Strategy

The clinical development program consisted of 8 studies (6 phase 2 studies and 3 phase 3 studies) in which 1472 subjects were exposed to sofpironium bromide, 871 of whom were treated at the 15% strength, and 643 with the intended marketed formulation.

The early, original formulation contained (b) (4) This excipient was replaced. The newer reformulation substituted isopropyl myristate (IPM), which is regarded as a generally recognized as safe (GRAS) ingredient. IPM1 was the SB 15% product intended for marketing in this application. A third SB formulation (IPM2), (b) (4)

Eight studies enrolled subjects with primary axillary hyperhidrosis who were treated with the sofpironium bromide gel (IPM1) intended for commercial formulation. The Applicant proposes sofpironium gel IPM1 formulation to provide data for labeling.

The phase 3, pivotal trials conducted using the to-be-marketed sofpironium gel 15% formulation were BBI-4000-CL-301 (301) and BBI-4000-CL-302 (302).

For long-term data, BBI-4000-CL-303 (303) was an open-label (OL), 52-week, long-term study in adults (SB 5% and 15%). This study enrolled treatment-naïve subjects who were not enrolled in trials 301 or 302.

Additional studies were conducted during which subjects were exposed to sofpironium bromide (SB) gel 15% (IPM1).

- BBI-4000-CL-102: phase 1, maximum use, PK study
- BBI 4000-CL-105: OL Sofpironium Bromide Gel, 15%, children and adolescents, ≥ 9 to <17 Years of Age
- BBI-4000-CL-108: OL, long-term study in children and adolescents ≥ 9 years to < 17 years (from Study 105)
- BBI-4000-03: Randomized, double-blind, repeat dose (SB 0%, 5%, 10%, 15%)
- BBI-4000-05: OL, 14-day, repeat dose, SB 15%, two formulations (IPM1 and IPM2)
- BB-4003-CL-203: Randomized, double-blind, dose-ranging (SB 5%, 10%, 15% and vehicle)

During the course of the studies, five subjects were identified as enrolling/screening at more than one site in one study, or in both studies 301 and 302. Four of these subjects were randomized a total of 10 times (10 unique subject IDs). Efficacy analyses were conducted both including and excluding these subjects. For safety, they were classified as duplicate subjects and noted in the individual study subject listings.

The Applicant provided definitions for the following populations:

- The Safety population was all subjects randomized in the study who received study drug, either vehicle or sofpironium bromide, 15%, at least once.
- The Intent-to-treat (ITT) population included all subjects randomized, including subjects with duplicate enrollments either within (301), or across (301) and (302).
- The modified intent-to-treat (mITT) population was a subset of the ITT population that excluded subjects with duplicate enrollments either within (301), or across (301) and (302).
- The per-protocol (PP) population was a subset of the mITT population, consisting of subjects who met specific criteria:

1. Met all inclusion/exclusion criteria
2. Had not taken or applied any interfering concomitant medications
3. Completed visits and collected data as specified

The subjects with duplicate enrollments were retained and the safety events included in the analyses. The Applicant analyzed the data using the ITT population or safety population.

- duplicate subjects with repeat registrations in the same study had each registration analyzed as a different study subject with his/her unique subject identifier
- duplicate subjects who registered in both BBI-4000-CL-301 and BBI-4000-CL-302, had registrations remain as they were for each of the respective studies.

Efficacy results were analyzed according to the planned randomized treatment. The primary analysis population was the ITT population, which includes the duplicate enrollments. The analysis based on the mITT population (which excludes the subjects with duplicate enrollments was supportive.

Subject safety data were analyzed according to the treatment actually received. This safety review will focus on the primary safety data, i.e., phase 3, pivotal trials 301 and 302, which was the focus of the Applicant's safety analyses. Additionally, discussion in this safety review pertains to the pivotal trials, unless otherwise specified, with the following exceptions: deaths, serious adverse events, and pregnancies. Generally, the safety review will only discuss comparisons between the sofpironium bromide 15% and vehicle groups in the phase 3 studies.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study BBI-4000-CL-301 (“Cardigan I “) and BBI-4000-CL-302 (“Cardigan II"): A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Topically Applied Sofpironium Bromide Gel, 15% in Subjects with Axillary Hyperhidrosis

Trial Design

Protocol BBI-4000-CL-301 (Cardigan I Study) and Protocol BBI-4000-CL-302 (Cardigan II Study) were studies of identical design conducted to support efficacy and safety of sofpironium bromide (SB) gel for the primary axillary hyperhidrosis indication. During this review, BBI-4000-CL-301 and BBI-4000-CL-302 will be known as 301 and 302, respectively. The trials’ design was multicenter, randomized, double-blind, and vehicle controlled. Subjects were evaluated at Screening (Visit 1), Pre-baseline (Visits 2 and 3, both within 14 days of baseline), Baseline/Day 1 (Visit 4), Day 8 (Visit 5), Day 15 (Visit 6), Day 22 (Visit 7), Day 29 (Visit 8), Day 36 (Visit 9), Day 41 (Visit 10), Day 42 (Visit 11), Day 43 (Visit 12), and Day 57/Follow-up (Visit 13). The trials enrolled subjects 9 years of age and older with a diagnosis of primary axillary hyperhidrosis. Subjects were to have

- Hyperhidrosis Disease Severity Measure-Axillary 7-item (HDSM-Ax-7) scale score of 3 to 4 inclusive at Visits 1 and 4
- A minimum of 50 mg of sweat production at rest (gravimetric test) in each axilla with a two-axilla combined total of at least 150 mg of sweat production in 5 minutes at room temperature at Screening Visit 1 and at least one of Visits 2, 3, or 4.
- Symptoms of axillary hyperhidrosis for ≥6 months’ duration

Each trial was designed to enroll approximately 350 subjects randomized in a 1:1 ratio to sofpironium bromide gel 15% or vehicle. Randomization was stratified by study site. All study sites were located in the United States. Subjects were to apply treatment once daily at bedtime to each axilla for 42 days.

Study Endpoints

Efficacy was assessed using the HDSM-Ax-7 scale score and gravimetric sweat assessments (5 minutes at room temperature) on both axillae.

The protocols defined the following co-primary endpoints:

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT)
- The change in gravimetric sweat production (GSP) from baseline to EOT

The protocols defined the following three secondary endpoints:

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to EOT.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT and achieving at least a 70% reduction in GSP from baseline to EOT.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to EOT and achieving at least a 50% reduction in GSP from baseline to EOT.

Note that subjects aged 12 and older and subjects 9 to <12 years of age used different versions of the HDSM-Ax instrument to generate the HDSM-Ax-7 scale score. A description of the instruments are as follows:

- HDSM-Ax – Adult Version
  The HDSM-Ax – Adult Version (Appendix 19.5) is an 11-item patient-reported outcome (PRO) instrument designed to assess the severity and frequency of excessive underarm sweating in participants 12 years of age and older. Each item is rated on a five-point verbal rating scale (VRS) with varied descriptors ranging from 0 (“I did not experience this” or “None of the time”) to 4 (“Very severe” or “All of the time”). The recall period is “since you woke up yesterday.”

- HDSM-Ax – Child Version
  The HDSM-Ax –Child Version (Appendix 19.5) is an 11-item PRO instrument designed to assess the amount and frequency of excessive underarm sweating in participants 9 to 11 years of age. Each item is rated on a five-point VRS ranging from 0 (“None of the time” or “I did not have this”) to 4 (“All of the time” or “A great amount”). The recall period is “since you woke up yesterday.”

A subset of 7 items from the HDSM-Ax instrument (Adult and Child versions) are used to compute the HDSM-Ax-7 scale score. The HDSM-Ax-7 scale score is calculated as the mean of the following 7 items: 1a, 1b, 2a, 2b, 2c, 2d, and 2e. The mean score ranged from 0 (indicating no severity) to 4 (indicating greatest severity).

Statistical Analysis Plan

The ITT population was defined as all randomized subjects. During the conduct of Studies 301 and 302, 4 subjects were identified as having been randomized multiple times into one or both of the studies at different sites (3 subjects who were randomized twice, and 1 subject who was randomized 4 times). The Statistical Analysis Plan (SAP) defined a modified intent-to-treat (mITT) population that excludes the subjects who had duplicate enrollments at multiple sites. The ITT population was used as the primary analysis population with the mITT population as supportive.

Subjects were to have gravimetric assessments at Screening (Visit 1), Visits 2 and 3 (both within 14 days of baseline), Baseline Day 1(Visit 4), and Days 8 (Visit 5), 15 (Visit 6), 22 (Visit 7), 29 (Visit 8), 36 (Visit 9), 41 (Visit 10), 42 (Visit 11), 43 (Visit 12), and 57 (Visit 13). Subjects were to complete the HDSM-Ax-7 at Screening (Visit 1), Baseline/Day 1 (Visit 4), and Visits 5 through 13.

The HDSM-Ax-7 scale response endpoint (at least a 2-point improvement from baseline to EOT) was to be analyzed using logistic regression with terms for treatment, baseline score, and analysis center. Both the questionnaires for subjects ≥9 to <12 and ≥12 years of age were to be used in the analysis. The assessment from Baseline/Day 1 (Visit 4) was to be used for the baseline value and the assessment from Day 43 (Visit 12) was to be used for the EOT value. If the subject is missing the baseline assessment, the screening (Visit 1) assessment was to be used. If the subject is missing the Day 43 assessment, the closest assessment from Day 42 or Day 41 was to be used. If none of the assessments from Days 41, 42, and 43 are available, multiple imputations of missing EOT (i.e. Day 43) item-level scores were to be performed.

The GSP change from baseline endpoint was to be analyzed with ANCOVA with terms for treatment, baseline GSP, and analysis center. A Shapiro-Wilk's test was to be conducted on the residuals to assess normality. If the assumption of normality is violated in either treatment arm, the analysis was to be conducted on the ranks. Because GSP values can be highly variable, the baseline score was defined as the median of values from Visits 2, 3, and 4, where Visit 4 is Day 1 and Visits 2 and 3 should be within 14 days prior to Visit 4/Day 1. The EOT value was to be the median of values from Visits 10, 11, and 12, corresponding to Days 41, 42, and 43. If the ranked analysis is used, the GSP data was to be ranked separately at each of Visits 2, 3, and 4; the median of the three ranks was to be used as baseline value of the subject. The EOT data was to be handled similarly using the ranks for Visits 10, 11, and 12. The difference between the rank-transformed baseline and EOT GSP values (EOT - baseline) was to serve as the outcome value for the rank-based GSP ANCOVA analysis. Missing EOT GSP data for each of Days 41, 42, and 43 was to be imputed before analysis is performed for subjects missing both axillae at all 3 visits. If at least one axillae is non-missing at Day 41, 42, or 43, then the EOT value was to be considered non-missing.

Reviewer Comment:
The protocol specified that for the rank-based analysis, ranks would be calculated for the baseline and EOT values separately, and that the analysis would be conducted on the 'difference of the ranks'. Note that for means, the 'difference of the means' and 'mean of the differences' are equivalent. However this equivalence does not hold for the 'difference of the ranks' versus the 'ranks of the differences,' due to the non-linearity of the ranking function. For an analysis with a covariate for the ranked baseline value in the model, the analysis for the 'difference of the ranks' is equivalent to an analysis of the ranks of the EOT values, as long as the model is adjusted for the baseline ranks. Thus, either an analysis of the 'difference of the ranks' and the 'ranks of the differences' may be reasonable, but the interpretation may be slightly different. This reviewer has included an analysis of the 'ranks of the differences' in the study results

section for comparison.

The binary secondary endpoints were analyzed comparably to the HDSM-Ax-7 scale response endpoint. For the multicomponent endpoints, both the HDSM-Ax-7 scale score and GSP baseline values were to be included in the model.

Multiple imputation was to be used to impute missing HDSM-Ax-7 scale scores and GSP values at EOT. Missing data on the sofpironium and vehicle arms was to be handled differently. Missing data on the vehicle arm was to use the Missing at Random (MAR) assumption. Missing data on the sofpironium arm was to be handled using a missing not a random (MNAR) assumption using a control-based imputations (CBI) model. This model assumes a subject's efficacy trajectory after dropping out would be similar to that of a subject on vehicle with similar characteristics and endpoint history. To reduce the impact of outlier values for the GSP endpoint on the multiple imputation sampling database, data from subjects who are more than 3 standard deviations away from the mean for the two arms combined was to be removed from the sampling database. Once the initial group of outliers have been removed, the mean and standard deviation was to be recalculated and the process of identifying values more than 3 standard deviations from the mean was to be repeated. This process was to be repeated until no more values meet the criteria. This approach is intended so that outlier values are not propagated during imputation. Note that the observed outlier values were to be used in the analysis, but those values were not to be part of the database used to impute missing data. The multiple imputation model was to use 20 imputations.

The following additional sensitivity analyses were planned for alternate handling of missing data. For HDSM-Ax-7 scale response, an observed case analysis and an analysis where missing data was to be imputed as non-responders were planned. A tipping point analysis using multiple imputations was also planned. An analysis of the influence of the 7 individual items in the HDSM-Ax-7 scale score were also planned. For the GSP change endpoint, an observed case analysis and an analysis with the outlying data removed were planned.

To control multiplicity, if the co-primary endpoints were statistically significant, the three secondary efficacy endpoints were analyzed sequentially in the order listed above.

Protocol Amendments

All subjects in Protocols 301 and 302 were enrolled under the final protocol version (Amendment 3). No protocol changes were made after subjects were enrolled. Because 5 subjects were discovered to have enrolled at multiple centers in the two studies, including 4 subjects who were randomized 2 or more times, one change was made to the statistical analysis plan to define the supportive mITT population that excludes any subject that was randomized more than once.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the trials were conducted using Good Clinical Practice according to the ethical principles founded in the Declaration of Helsinki, and guidelines and principles according to the International Council on Harmonisation Tripartite Guideline.

Financial Disclosure

The Applicant certified that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (list of names was included) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

In accordance with 21 CFR part 54, the Applicant submitted Form 3455 for one investigator who participated in Study 301. This individual had participated in financial arrangements or held financial interests that were required to be disclosed as follows: any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. No other details were provided.

Patient Disposition

Study 301 randomized 350 subjects at 35 centers in the U.S. One subject was withdrawn from the study before receiving any treatment because the subject did not meet eligibility criteria. Study 302 randomized 351 subjects at 33 centers in the U.S. The ITT population includes all randomized subjects. Four subjects were randomized multiple times in either Study 301 or 302 at different centers. These 4 subjects account for 10 randomizations across the two studies. These 4 subjects are excluded from the mITT population. See additional discussion of these multiple enrollments under the Data Quality and Integrity section. In Study 301, 13% of SB gel subjects and 8% of vehicle subjects discontinued the study. In Study 302, 11% of SB gel subjects and 9% of vehicle subjects discontinued the study. The most common reasons for study discontinuation were loss to follow-up, withdrawal by subject, and adverse events. All subjects who discontinued due to adverse events were on the SB gel arm. See Table 15.

Table 15 – Disposition of Subjects (Studies 301 and 302)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
ITT[1], n (%)	173 (100)	177 (100)	180 (100)	171 (100)
MITT[2], n (%)	169 (98)	173 (98)	180 (100)	169 (99)
Safety Population[3], n (%)	173 (100)	176 (99)	180 (100)	171 (100)
Discontinued treatment, n (%)	19 (11)	10 (6)	19 (11)	13 (8)
Discontinued study, n (%)	23 (13)	15 (8)	20 (11)	16 (9)
Reason for study discontinuation, n (%)				
Adverse event	5 (3)	0 (0)	9 (5)	0 (0)
Lost to follow-up	10 (6)	8 (5)	4 (2)	8 (5)
Other	1 (1)	0 (0)	0 (0)	0 (0)
Physician decision	0 (0)	0 (0)	1 (1)	0 (0)
Pregnancy	1 (1)	0 (0)	0 (0)	0 (0)
Protocol violation	2 (1)	3 (2)	0 (0)	2 (1)
Withdrawal by subject	4 (2)	4 (2)	6 (3)	6 (4)

[1] All randomized subjects (includes subjects with multiple randomizations)
[2] All subjects who were randomized only once
[3] Randomized and treated subjects (includes subjects with multiple randomizations)
Source: Clinical Study Report 301 (page 52) and Clinical Study Report 302 (page 54); findings reproduced by the statistical reviewer using adsl.xpt.

Protocol Violations/Deviations

The proportion of subjects who had major protocol deviations was similar on the SB gel and vehicle arms in both studies. The most common protocol deviations were informed consent non-compliance and inclusion/exclusion criteria violations. See Table 16. The subjects who had multiple enrollments are described in the Data Quality and Integrity section below.

Table 16 – Major Protocol Deviations in Studies 301 and 302 (Safety Population)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=176)	SB Gel 15% (N=180)	Vehicle (N=171)
Any major protocol deviation	20 (11.6)	18 (10.2)	7 (3.9)	6 (3.5)
Informed consent non-compliance	15 (8.7)	10 (5.7)	4 (2.2)	4 (2.3)
Inclusion/exclusion criteria	6 (3.5)	8 (4.5)	1 (0.6)	2 (1.2)
Assessment done by staff not delegated/trained	0	1 (0.6)	0	0
GCP related	0	0	1 (0.6)	0
Prohibited concomitant medication	1 (0.6)	0	1 (0.6)	0

Source: Clinical Study Report 301 (page 56) and Clinical Study Report 302 (page 58); findings reproduced by the statistical reviewer using dv.xpt.

Table of Demographic Characteristics

Baseline demographic characteristics were generally balanced across treatment arms in both studies. The studies enrolled slightly more female subjects than male subjects. Most subjects were between 18 and 64 years of age (91%). Less than 1% of subjects were 10 or 11 years of age, 7% of subjects were 12 to 17 years of age, and 1% of subjects were 65 years of age or older. The majority of subjects were white (78%), 20% were Black or African American, 1% were Asian, and less than 1% were American Indian or Alaska Native. Approximately 31% of subjects were Hispanic or Latino. See Table 17.

Table 17 – Baseline Demographics in Studies 301 and 302 (ITT)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
Age (years)				
N	173	177	180	171
Mean (SD)	32.9 (11.6)	32.4 (10.9)	32.1 (12.2)	31.7 (11.1)
Range	11, 64	14, 71	10, 76	11, 69
Age Group, n (%)				
9-11 years	1 (1)	0 (0)	2 (1)	2 (1)
12-17 years	14 (8)	12 (7)	13 (7)	8 (5)
18-64 years	158 (91)	163 (92)	161 (89)	158 (92)
≥65 years	0 (0)	2 (1)	4 (2)	3 (2)
Sex, n (%)				
Female	98 (57)	99 (56)	92 (51)	103 (60)
Male	75 (43)	78 (44)	88 (49)	68 (40)
Race[1], n (%)				
American Indian or Alaska Native	0 (0)	0 (0)	2 (1)	1 (1)
Asian	1 (1)	3 (2)	4 (2)	1 (1)
Black or African American	31 (18)	43 (24)	32 (18)	34 (20)
White	140 (81)	130 (73)	141 (78)	133 (78)
Unknown or not reported	1 (1)	1 (1)	1 (1)	2 (1)
Ethnicity, n (%)				
Hispanic or Latino	61 (35)	60 (34)	48 (27)	45 (26)
Not Hispanic or Latino	111 (64)	117 (66)	132 (73)	124 (73)
Not reported	1 (1)	0 (0)	0 (0)	2 (1)

[1] Predominant race if multiple races selected
Note: the ITT population includes duplicate subject enrollments.
Source: : Clinical Study Report 301 (page 58) and Clinical Study Report 302 (page 60); findings reproduced by the statistical reviewer using adsl.xpt.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Subjects were to have HDSM-Ax-7 scale scores of 3 to 4 at screening and baseline. Baseline HDSM-Ax-7 scale scores were balanced across treatment arms in both studies. The mean baseline gravimetric sweat production values were similar across both treatment arms in both studies, though the median values were slightly higher on the vehicle arm than the SB gel arm in both studies. The duration of symptoms of axillary hyperhidrosis was similar on the SB gel and vehicle arms in Study 301, and slightly higher on the SB gel arm in Study 302. See Table 18.

Table 18 – Baseline Disease Characteristics in Studies 301 and 302 (ITT)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
HDSM-Ax-7[1]				
Mean (SD)	3.5 (0.3)	3.5 (0.3)	3.6 (0.3)	3.6 (0.3)
Median	3.4	3.6	3.6	3.6
Range	3.0, 4.0	2.9, 4.0	3.0, 4.0	3.0, 4.0
GSP[2] (mg)				
Mean (SD)	296.2 (257.1)	298.5 (223.4)	313.8 (283.7)	308.4 (267.2)
Median	214.1	228.6	207.7	231.1
Range	38.4, 1512.1	20.4, 1523.8	38.6, 1773.6	8.9, 2356.6
Duration of Symptoms (months)				
Mean (SD)	179.3 (115.2)	184.4 (116.9)	202.6 (131.9)	194.4 (117.3)
Median	156.3	157.2	193.6	172.4
Range	6.5, 564.7	19.9, 588.6	9.1, 712.0	16.5, 495.4

[1] Baseline/Day 1 (Visit 4) assessment
[2] The baseline GSP value is the median of observations on Visits 2, 3, and 4 (Baseline/Day 1). Visits 2 and 3 were to be within 14 days prior to Baseline/Day 1.
Source: Reviewer analysis using Applicant submitted datasets adhdsm.xpt, adgsp.xpt, and adsl.xpt.

Treatment Compliance, Concomitant Medications Use

The duration of treatment was similar on the SB gel and vehicle arms in both studies. Duration of treatment was defined as the Date of last dose – Date of first dose + 1 and does not account for missed doses. The planned treatment duration was 42 days. See Table 19.

Table 19 – Duration of Treatment in Studies 301 and 302 (Safety Population)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=176)	SB Gel 15% (N=180)	Vehicle (N=171)
Duration of Treatment (days)				
Mean (SD)	42.5 (8.9)	44.1 (8.5)	41.8 (8.9)	42.2 (9.1)
Range	1, 65	1, 84	1, 57	1, 69

Source: Clinical Study Report 301 (page 95) and Clinical Study Report 302 (page 97)

Concomitant Medications

The Applicant defined a prior medication as any medication started prior to the date of the first dose of study drug. The majority of subjects reported use of any prior medication across both study drug and vehicle arms in both pivotal trials. Of note, there was low use of corticosteroids of moderate potency (Class II), which was less than 5%.

Table 20 - Summary of Prior Medications by Drug Class, Safety Population

	Trial BBI-400-CL-301		Trial BBI-400-CL-302	
	Vehicle N=176 n (%)	SB 15% N=173 n (%)	Vehicle N=171 n (%)	SB 15% N=180 n (%)
Any Prior Med	95 (54.0)	88 (50.9)	91 (53.2)	104 (57.8)
Corticosteroids, Mod. Potency (Group II)	2 (1.1)	2 (1.2)	1 (0.6)	4 (2.2)
COVID-19 Vaccines	3 (1.7)	2 (1.2)	13 (7.6)	9 (5.0)
Progestogens/Estrogens, Fixed combinations	16 (9.1)	24 (13.9)	15 (8.8)	19 (10.6)
Intrauterine Contraceptives	14 (8.0)	4 (2.3)	13 (7.6)	15 (8.3)
SSRI	12 (6.8)	6 (2.5)	5 (2.9)	10 (5.6)
Other antidepressants[1]	8 (4.5)	12 (6.9)	12 (7.0)	14 (7.8)
Propionic acid derivatives[2]	2 (1.1)	4 (2.3)	2 (1.1)	4 (2.3)
Piperazine derivatives[3]	4 (2.3)	3 (1.7)	3 (1.8)	15 (8.3)
Centrally acting sympathomimetics[4]	3 (1.7)	7 (4.0)	9 (5.3)	11 (6.1)

SB= sofpironium bromide; SSRI=selective serotonin reuptake inhibitors; Mod=moderate
[1] bupropion, lamotrigine, venlafaxine, duloxetine, oxitriptan
[2] ibuprofen, naproxen, naproxen sodium;
[3] cetirizine, levocetirizine

[4] lisdexamfetamine mesylate, amfetamines, methylphenidate hydrochloride, atomoxetine, dexmethylphenidate
Adapted from Table 14.1.5, Reports 301 and 302

The Applicant defined a concomitant medication as any medication started on or after the date of the first dose of study drug. The majority of subjects reported use of "any concomitant medication" across both study drug and vehicle arms in both pivotal trials. Corticosteroids moderate potency (Group II) reported the highest change from prior medication use reports and the greatest difference between SB and vehicle. The other medications such as progestogens/estrogens, fixed combinations and intrauterine devices showed no change in reported use during the clinical trials. While some reports were greater than 5%, the concomitant use for selective serotonin reuptake inhibitors (SSRIs), piperazine derivatives, propionic acid derivatives, centrally acting sympathomimetics, and other antidepressants showed minor changes.

Table 21 - Summary of Concomitant Medications by Drug Class > 5%, Safety Population

	Trial BBI-400-CL-301		Trial BBI-400-CL-302	
	Vehicle N=176 n (%)	SB 15% N=173 n (%)	Vehicle N=171 n (%)	SB 15% N=180 n (%)
Any Concomitant Med	100 (56.8)	103 (59.5)	95 (55.6)	113 (62.8)
Corticosteroids, Mod. Potency (Group II)	1 (0.6)	18 (10.4)	5 (2.9)	21 (11.7)
COVID-19 Vaccines	16 (9.1)	15 (13.9)	9 (5.3)	4 (2.2)
Progestogens/Estrogens, Fixed combinations	16 (9.1)	24 (13.9)	15 (8.8)	19 (10.6)
Intrauterine Contraceptives	14 (8.0)	4 (2.3)	13 (7.6)	15 (8.3)
SSRI	13 (7.4)	6 (2.5)	5 (2.9)	10 (5.6)
Other antidepressants[1]	8 (4.5)	12 (6.9)	12 (7.0)	15 (8.3)
Propionic acid derivatives[2]	3 (1.7)	2 (1.2)	8 (4.7)	10 (5.6)
Piperazine derivatives[3]	4 (2.3)	3 (1.7)	3 (1.8)	16 (8.9)
Centrally acting sympathomimetics[4]	3 (1.7)	5 (2.9)	9 (5.3)	11 (6.1)

SB= sofpironium bromide; SSRI=selective serotonin reuptake inhibitors; Mod=moderate
[1] bupropion, lamotrigine, venlafaxine, duloxetine, oxitriptan
[2] ibuprofen, naproxen, naproxen sodium;
[3] cetirizine, levocetirizine
[4] lisdexamfetamine mesylate, amfetamines, methylphenidate hydrochloride, atomoxetine,dexmethylphenidate
Adapted from Table 14.3.6.5 in Reports 301 and 302

Reviewer comments: There is a 4- to 18-fold difference in concomitant corticosteroid use for both trials, greater in the study drug arm than vehicle. Since corticosteroid use prior to study drug use was comparable, it is considered possible that corticosteroid use is related to study drug use.
The other drugs reported for concomitant use showed no change, or minor increases and decreases with no consistent pattern, so that no correlation with study drug use could be determined.

Efficacy Results – Primary Endpoint

Studies 301 and 302 had co-primary endpoints of ≥2 point improvement in the HDSM-Ax-7 scale score from baseline to EOT and change in gravimetric sweat production from baseline to EOT. The primary analysis population was the ITT population, which included all randomized subjects including those with multiple enrollments. The mITT population that excluded subjects with multiple enrollments was supportive.

HDSM-Ax-7 Scale Score

The proportion of subjects with ≥2 point improvement in the HDSM-Ax-7 scale score from baseline to EOT was analyzed with logistic regression with terms for treatment, baseline score, and analysis center. Confidence intervals for the treatment difference were estimated using the Wald method without covariate adjustment. Missing data was handled with multiple imputation. SB gel was superior to vehicle for the HDSM-Ax-7 scale response endpoint for the protocol-specified analysis in the ITT population in both studies (p=0.0004 in Study 301 and p=0.0029 in Study 302). The vehicle response rate was higher in Study 302 than in Study 301, though the treatment difference estimates were similar for the two studies (18.6% vs. 16.6%). The results for the mITT population were very similar to the results for the ITT population. Because subjects who were ≥9 to <12 years of age and subjects who were ≥12 years of age used two different HDSM-Ax instruments to generate the HDSM-Ax-7 scale score, results only for subjects ≥12 years of age (HDSM-Ax-7 – Adult Version) are also presented, as it is inappropriate to pool data from these two instruments into a single endpoint. See Table 22. Too few subjects ≥9 to <12 years of age were enrolled to adequately evaluate HDSM-Ax-7 response in that subgroup; however, the data from subjects ≥9 to <12 years of age were looked at descriptively (see Table 27 below).

Table 22 – Percentage of Subjects with **≥2** point improvement in the HDSM-Ax-7 Scale Score in Studies 301 and 302

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
ITT	N=173	N=177	N=180	N=171
Estimated proportion (adjusted[1]) (%)	49.3	29.3	63.9	47.0
p-value	0.0004		0.0029	
Estimated proportion (unadjusted[2]) (%)	50.7	32.1	63.1	46.6
Treatment difference (95% CI)	18.6 (8.3, 28.9)		16.6 (5.9, 27.2)	
mITT	N=169	N=173		

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
Estimated proportion (adjusted[1]) (%)	49.1	28.9	64.6	47.5
p-value	0.0003		0.0022	
Estimated proportion (unadjusted[2]) (%)	50.3	31.8	63.8	46.9
Treatment difference (95% CI)	18.5 (8.1, 28.8)		16.9 (6.3, 27.4)	
ITT (Subjects **≥12** years)	N=172	N=177	N=178	N=169
Estimated proportion (adjusted[1]) (%)	48.8	29.3	64.2	47.7
p-value	0.0005		0.0040	
Estimated proportion (unadjusted[2]) (%)	50.4	32.1	63.3	47.1
Treatment difference (95% CI)	18.3 (8.0, 28.7)		16.2 (5.4, 26.9)	

[1] Estimates from logistic regression adjusted for baseline and analysis center.
[2] Estimates and CI using Wald method
CI= confidence interval
Source: Clinical Study Report 301 (page 62) and Clinical Study Report 302 (page 64); findings reproduced by the statistical reviewer using adhdsmi.xpt.

Missing Data Handling

The applicant conducted a tipping point analysis to evaluate the impact of missing data. For this analysis, multiple imputation was used to impute the change from baseline in HDSM-Ax-7 scale score (EOT-Baseline) for subjects with missing data. A shift parameter ranging from 0.5 to 3 units (delta) was added to the imputed value for SB gel subjects and subtracted from vehicle subjects (i.e., each treatment arm penalized towards 'no difference'). In Study 301, the analysis did not tip ($p<0.05$), even if 3 units were added to the subjects with missing data on the active arm and 3 units were subtracted from the subjects with missing data on the vehicle arm. In Study 302, the analysis tipped ($p>0.05$) when 1 unit was added to the subjects with missing data on the active arm and 1 unit was subtracted from the subjects with missing data on the vehicle arm. See Table 23.

Table 23 – Tipping Point Analysis for Response on the HDSM-Ax-7 Scale Score in Study 301 and 302 (ITT)

	Study 301			Study 302		
	SB Gel 15% (N=173) (%)	Vehicle (N=177) (%)	P-value	SB Gel 15% (N=180) (%)	Vehicle (N=171) (%)	P-value
Missing data	9.2	6.2		10.0	7.0	
Shift parameter						
0	49.3	29.3	0.0004	63.9	47.0	0.0029
0.5	47.2	31.2	0.0035	61.4	49.4	0.0292
1	46.8	32.3	0.0116	60.9	51.0	0.0703
1.5	46.8	33.7	0.0168			

	Study 301			Study 302		
	SB Gel 15% (N=173) (%)	Vehicle (N=177) (%)	P-value	SB Gel 15% (N=180) (%)	Vehicle (N=171) (%)	P-value
2	46.8	34.1	0.0198			
2.5	46.8	34.1	0.0201			
3	46.8	34.1	0.0201			

Source: Clinical Study Report 301 (page 792) and Clinical Study Report 302 (page 799); findings reproduced by the statistical reviewer using adhdsmi.xpt.

Thus, it is of interest to understand whether adding/subtracting 1 unit to the change from baseline values would lead to plausible values on the active and vehicle arms. The first row of Table 24 presents the mean change from baseline in HDSM-Ax-7 scale score among subjects with observed data. In Study 301, the mean change on the SB gel arm was about 0.5 units lower than that observed on the vehicle arm, and the difference was about 0.41 units in Study 302. The second row of Table 24 presents the mean imputed change from baseline values among subjects requiring data imputation due to missing data using the multiple imputation procedure specified in the protocol. Note that the planned procedure imputes similar values to subjects on each arm with missing data. The third row presents how the means for the imputed data would differ if 1 unit was added to the SB gel group and subtracted from the vehicle group, which is the situation in which Study 302 tipped into non-significance. Under this assumption, on average, subjects on the SB gel arm with missing data would perform about 1 unit worse than subjects receiving vehicle with observed data and subjects on the vehicle arm with missing data would perform about 1 unit better than subjects on the active arm with observed data. As these assumptions seem implausible, the missing data in Studies 301 and 302 did not have an impact on the conclusions regarding response on HDSM-Ax-7 scale score.

Table 24 – Impact of Delta in Tipping Point Analysis for Change from Baseline in the HDSM-Ax-7 Scale Score in Studies 301 and 302 (ITT)

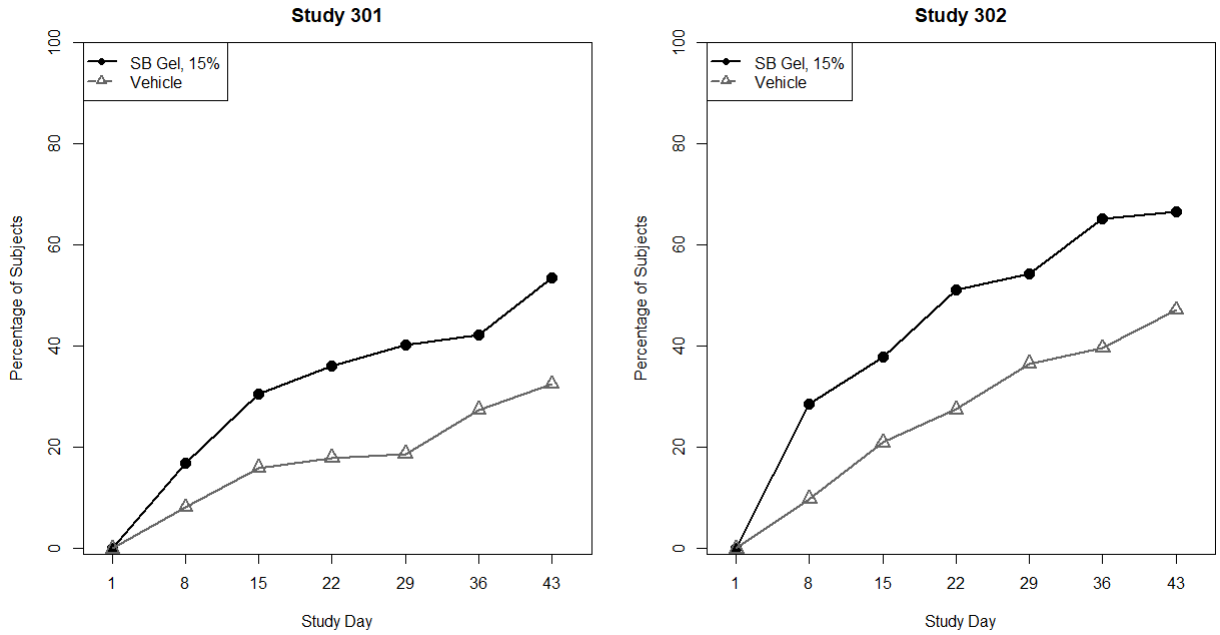
	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
Mean Change in HDSM-Ax-7 scale score (EOT-BL) for observed data	N=157 -1.94	N=166 -1.44	N=162 -2.19	N=159 -1.78
Mean Change in HDSM-Ax-7 scale score (EOT-BL) for imputed data (Original model; delta=0)	N=16 -1.57	N=11 -1.57	N=18 -1.76	N=12 -1.81
Mean Change in HDSM-Ax-7 (EOT-BL) for imputed data (Tipping model; delta=1)	N=16 -0.57	N=11 -2.57	N=18 -0.76	N=12 -2.81

Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt.

Efficacy over Time

The proportion of subjects with HDSM-Ax-7 scale response increased over time on both SB gel and vehicle throughout the study, though the proportion was consistently higher on the SB gel arm. See Figure 1.

Figure 1 – Percentage of Subjects with **≥2** point improvement in the HDSM-Ax-7 Scale Score by Visit in Studies 301 and 302 (Observed Cases)

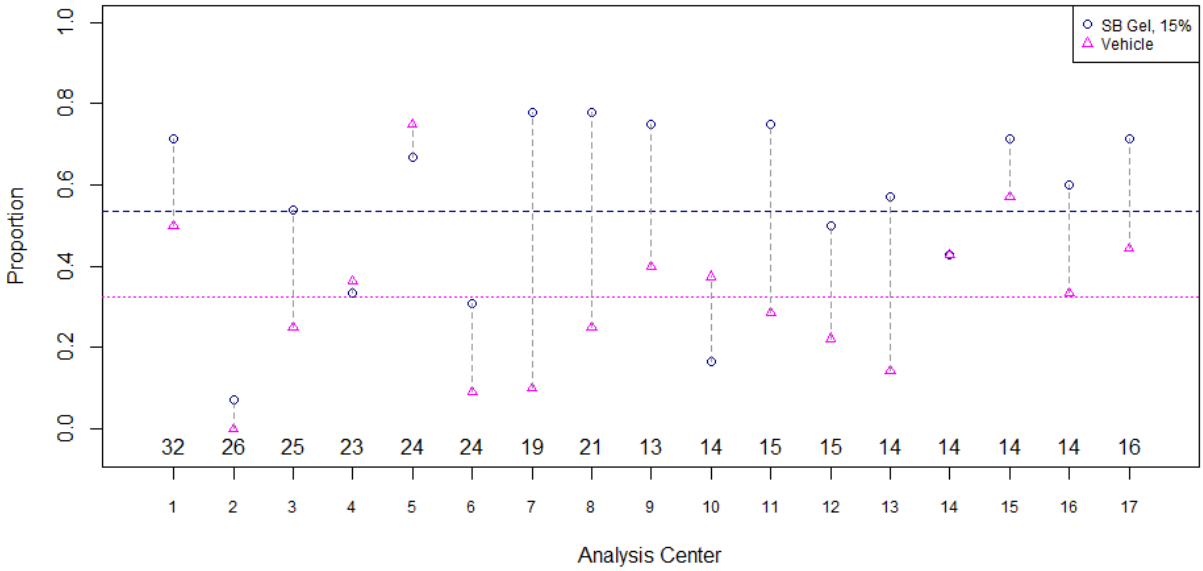


Source: Reviewer analysis using Applicant submitted datasets adhdsm.xpt.

Efficacy by Analysis Center

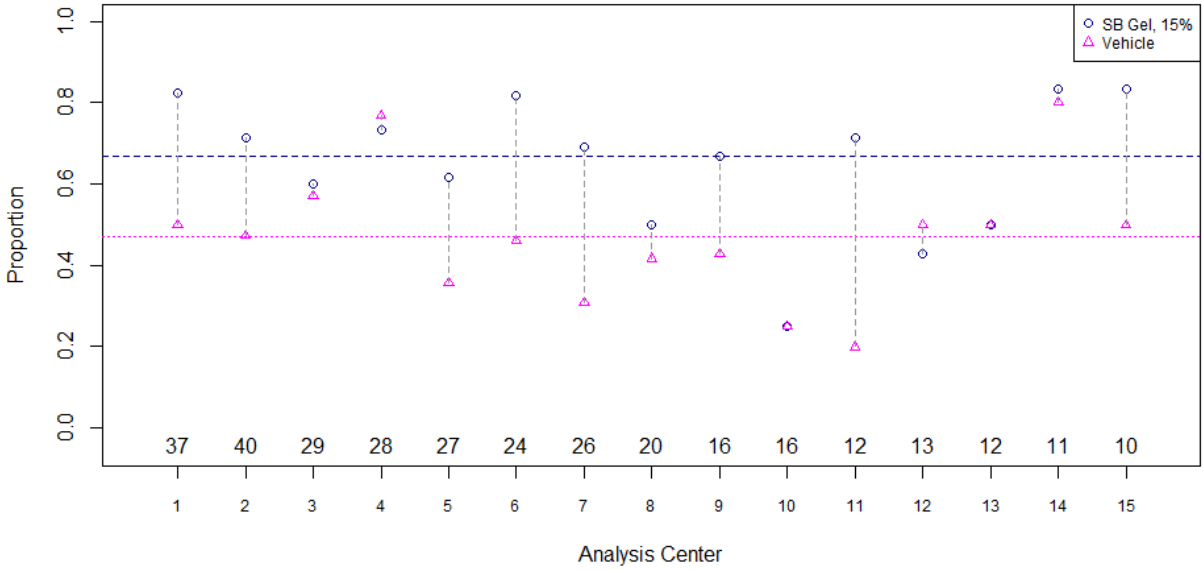
Study 301 randomized 350 subjects at 35 centers in the U.S. Study 302 randomized 351 subjects at 33 centers in the U.S. Many of the sites in both studies enrolled relatively few subjects. For the analysis, the protocol specified that small centers would be combined with larger center to create analysis center. For sites with <10 subjects, the lowest enrolling site was combined with the largest enrolling site, and then the second lowest enrolling site and the second largest enrolling site were combined, and so on. HDSM-Ax-7 scale response by analysis center is presented in Figure 2 and Figure 3. Treatment effects were generally consistent across analysis centers.

Figure 2 – Percentage of Subjects with **≥2** point improvement in the HDSM-Ax-7 Scale Score by Center in Study 301 (Observed Cases)



Numbers represent total number of subjects per analysis center
Source: Reviewer analysis using Applicant submitted datasets adhdsm.xpt.

Figure 3 – Percentage of Subjects with **≥2** point improvement in HDSM-Ax-7 Scale Score by Analysis Center in Study 302 (Observed Cases)



Numbers represent total number of subjects per analysis center
Source: Reviewer analysis using Applicant submitted datasets adhdsm.xpt.

Findings in Subgroup Populations

Treatment effects across demographic subgroups were somewhat variable in the two studies, though the response rates for SB gel were generally larger than for vehicle in each subgroup. When considering the subgroup analyses from the pooled studies, treatment effects were consistent across all moderately sized subgroups, except that the treatment effect was larger for females than for males. See Table 25 through Table 27.

Table 25 – Percentage of Subjects with **≥2** point improvement in the HDSM-Ax-7 Scale Score by Demographic Subgroups in Study 301 (ITT)

	SB Gel 15% (N=173)	Vehicle (N=177)	Difference (95% CI)
Age Group, (n_1, n_2)[1] (%)			
[redacted] (b) (4)			
12-17 years (14, 12)	67.5	20.8	46.7 (11.1, 82.2)
≥18 years (158, 165)	48.9	32.9	16.0 (5.2, 26.8)
Sex, (n_1, n_2) (%)			
Female (98, 99)	57.7	33.6	24.0 (10.0, 38.0)
Male (75, 78)	41.6	30.1	11.5 (-3.9, 26.8)
Race[3], (n_1, n_2) (%)			
Black or African American (31, 43)	39.0	18.6	20.4 (-0.4, 41.3)
White (140, 130)	54.0	36.8	17.2 (5.3, 29.2)
Ethnicity, (n_1, n_2) (%)			
Hispanic or Latino (61, 60)	43.6	42.5	1.1 (-16.7, 18.9)
Not Hispanic or Latino (111, 117)	54.1	26.8	27.4 (14.8, 40.0)

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
[redacted] (b) (4)
[3] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
Note: the ITT population includes duplicate subject enrollments.
NA= not available; sample size too small for meaningful calculations
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt.

Table 26 – Percentage of Subjects with **≥2** point improvement in the HDSM-Ax-7 Scale Score by Demographic Subgroups in Study 302 (ITT)

	SB Gel 15% (N=180)	Vehicle (N=171)	Difference (95% CI)
Age Group, (n_1, n_2)[1] (%)			
[redacted] (b) (4)			
12-17 years (13, 8)	42.3	50.0	-7.7 (-52.2, 36.8)
≥18 years (165, 161)	64.9	47.0	18.0 (7.0, 28.9)
Sex, (n_1, n_2) (%)			
Female (92, 103)	66.8	43.8	23.0 (9.0, 37.0)

	SB Gel 15% (N=180)	Vehicle (N=171)	Difference (95% CI)
Male (88, 68)	59.3	50.7	8.5 (-7.7, 24.7)
Race[3], (n_1, n_2) (%)			
Black or African American (32, 24)	62.5	51.6	10.9 (-13.0, 34.8)
White (141, 133)	64.3	46.7	17.6 (5.5, 29.7)
Ethnicity, (n_1, n_2) (%)			
Hispanic or Latino (48, 45)	70.1	42.0	28.1 (8.5, 47.7)
Not Hispanic or Latino (132, 124)	60.6	48.5	12.1 (-0.4, 24.7)

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
(b) (4)

[3] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
Note: the ITT population includes duplicate subject enrollments.
NA= not available; sample size too small for meaningful calculations
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt

Table 27 – Percentage of Subjects with **≥2** point improvement in the HDSM-Ax-7 Scale Score by Demographic Subgroups in Pooled Studies 301 and 302 (ITT)

	SB Gel 15% (N=353)	Vehicle (N=348)	Difference (95% CI)
Age Group, (n_1, n_2)[1] (%)			
(b) (4)			
12-17 years (27, 20)	55.4	32.5	22.9 (-5.9, 51.6)
≥18 years (323, 326)	57.1	39.9	17.2 (9.5, 24.9)
Sex, (n_1, n_2) (%)			
Female (190, 202)	62.1	38.8	23.3 (13.4, 33.1)
Male (163, 146)	51.1	39.7	11.4 (0.2, 22.6)
Race[3], (n_1, n_2) (%)			
Black or African American (63, 77)	51.0	33.2	17.8 (1.5, 34.1)
White (281, 263)	59.2	41.8	17.4 (8.9, 25.9)
Ethnicity, (n_1, n_2) (%)			
Hispanic or Latino (109, 105)	55.3	42.3	13.0 (-0.4, 26.4)
Not Hispanic or Latino (243, 241)	57.7	37.9	19.7 (10.8, 28.7)

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
(b) (4)

[3] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
Note: the ITT population includes duplicate subject enrollments.
NA= not available; sample size too small for meaningful calculations
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt

Gravimetric Sweat Production

Based on the results of the Shapiro-Wilk's test ($p<0.0001$ for each treatment arm in each study), the protocol specified that the primary analysis for GSP change from baseline would be based on the ranks. The baseline rank score was calculated as the median of the ranks from Visits 2, 3, and 4, where Visit 4 is Day 1 and Visits 2 and 3 should be within 14 days prior to Visit 4/Day 1. The EOT rank value was the median of the ranks from Visits 10, 11, and 12, corresponding to Days 41, 42, and 43. The difference between the rank-transformed baseline and EOT GSP values (EOT – baseline) was the outcome value for the rank-based GSP ANCOVA analysis ('Difference in Ranks'). The ANOVA model used terms for baseline rank and analysis center. The primary efficacy analysis conducted using the difference in ranks for the ITT population was statistically significant in both studies ($p=0.0019$ for Study 301 and $p=0.0296$ for Study 302). See Table 28.

Rather than ranking the baseline and EOT values and calculating the difference in ranks, this reviewer also conducted a ranked analysis using the same model in which the change from baseline values were calculated on the original scale, and then the differences ranked ('Ranks of Differences'), rather than analyzing the difference in ranks. The results of this sensitivity analysis are also presented in Table 28, and the results were also statistically significant in each study.

The untransformed data was also analyzed with ANOVA with terms for baseline and analysis center as a sensitivity analysis. The results of this analysis were statistically significant in Study 302 ($p=0.0136$), but not in Study 301 ($p=0.5324$). Note that because of the skewness of the distribution, the results of the analysis of the untransformed data are not expected to be consistent with the ranked analysis that mitigates the impact of outliers.

The results for the MITT population for each of these analyses were also conducted as supportive analyses. The results in the MITT population were very similar to the comparable ITT population results. See Table 29.

Table 28 – Change from Baseline to End of Treatment[1] in Gravimetric Sweat Production in Studies 301 and 302 (ITT)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
ITT – Difference in Ranks[2, 3]	N=173	N=177	N=180	N=171
LS Means [Ranks] (SE)	-14.9 (6.8)	14.8 (6.7)	-9.9 (7.1)	11.8 (7.5)
Treatment difference (95% CI)	-29.7 (-48.4, -11.0)		-21.8 (-41.4, -2.2)	
p-value	0.0019		0.0296	
ITT –Ranks of Difference[3]				
LS Means [Ranks] (SE)	165.8 (6.1)	184.8 (6.0)	165.1 (5.4)	185.8 (5.7)
Treatment difference (95% CI)	-19.02 (-36.0, -2.1)		-20.7 (-35.7, -5.7)	

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
p-value	0.0281		0.0069	
ITT – Values[4]				
LS Means [Values] (SE)	-151.4 (13.3)	-139.8 (13.3)	-206.5 (9.8)	-173.6 (10.0)
Treatment difference (95% CI)	-11.6 (-48.0, 24.8)		-32.8 (-58.8, -6.8)	
p-value	0.5324		0.0136	
Median	-127.8	-100.3	-142.6	-134.2
25th percentile, 75th percentile	-200.5, -52.4	-227.5, -28.5	-260.1, -75.0	-230.0, -59.5

[1] Baseline value calculated from the median GSP value from Visits 2, 3, and 4; EOT value calculated from the median GSP value from Visits 10, 11, and 12.
[2] Protocol-specified primary analysis.
[3] ANOVA on ranks adjusted for baseline rank and analysis center (multiple imputation).
[4] ANOVA adjusted for baseline and analysis center (multiple imputation); Medians and quartiles averaged over the 20 multiply imputed datasets.
LS=Least squares; SE = standard error; CI= confidence interval
Source: Clinical Study Report 301 (page 173) and Clinical Study Report 302 (page 180); findings reproduced or conducted by the statistical reviewer using adgspmi.xpt.

Table 29 – Change from Baseline to End of Treatment[1] in Gravimetric Sweat Production in Studies 301 and 302 (MITT)

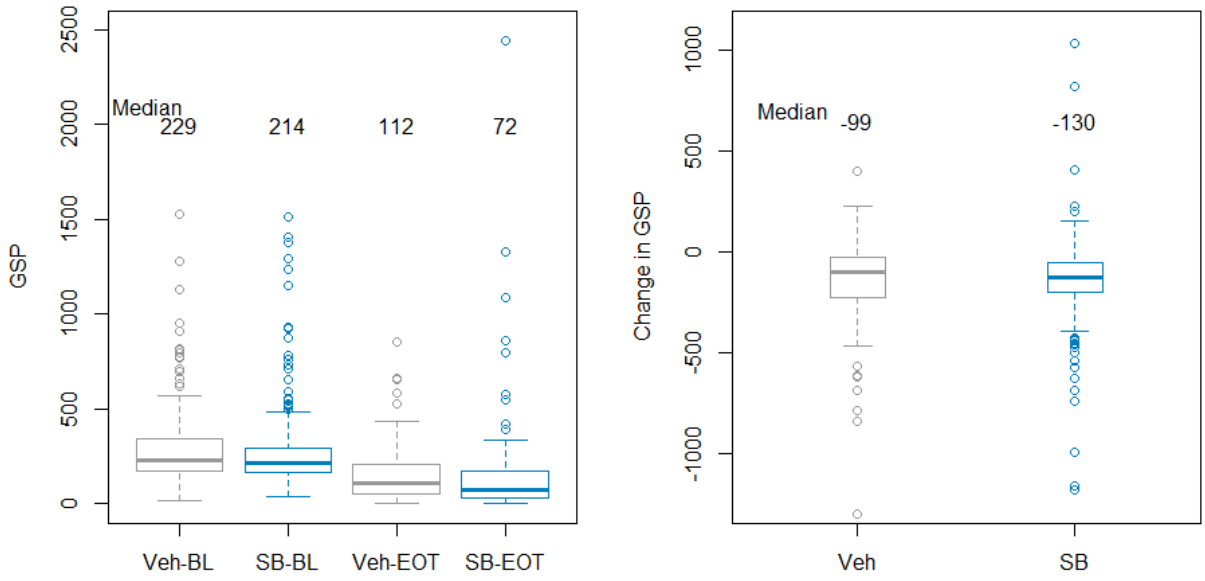
	Study 301		Study 302	
	SB Gel 15% (N=169)	Vehicle (N=173)	SB Gel 15% (N=180)	Vehicle (N=169)
MITT – Difference in Ranks[2]				
LS Means [Ranks] (SE)	-15.6 (6.8)	13.6 (6.7)	-10.7 (7.1)	11.6 (7.4)
Treatment difference (95% CI)	-29.2 (-48.2, -10.3)		-22.2 (-41.9, -2.6)	
p-value	0.0025		0.0266	
MITT –Ranks of Difference[2]				
LS Means [Ranks] (SE)	166.6 (6.2)	187.6 (6.1)	165.5 (5.4)	186.0 (5.7)
Treatment difference (95% CI)	-21.1 (-38.1, -4.0)		-20.5 (-35.5, -5.6)	
p-value	0.0156		0.0072	
MITT – Values[3]	N=169	N=173	N=180	N=169
LS Means [Values] (SE)	-147.8 (13.5)	-134.7 (13.4)	-206.8 (9.9)	-173.2 (9.9)
Treatment difference (95% CI)	-13.1 (-50.0, 23.8)		-33.6 (-59.7, -7.4)	
p-value	0.4853		0.0120	
Median	-126.3	-98.4	-142.6	-133.7
25th percentile, 75th percentile	-194.9, -52.6	-215.2, -25.3	-260.1, -75.0	-225.9, -60.3

[1] Baseline value calculated from the median GSP value from Visits 2, 3, and 4; EOT value calculated from the median GSP value from Visits 10, 11, and 12.
[2] ANOVA on ranks adjusted for baseline rank and analysis center (multiple imputation).

[3] ANOVA adjusted for baseline and analysis center (multiple imputation); Medians and quartiles averaged over the 20 multiply imputed datasets.
LS=Least squares; SE = standard error; CI= confidence interval
Source: Clinical Study Report 301 (page 173) and Clinical Study Report 302 (page 180); findings reproduced or conducted by the statistical reviewer using adgspmi.xpt.

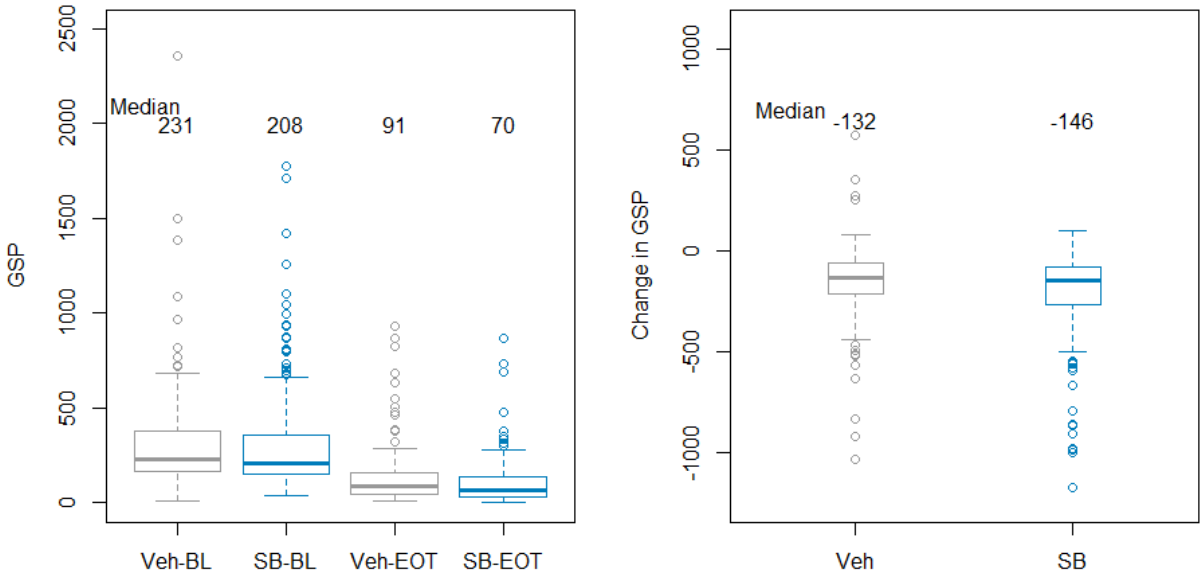
Figure 4 and Figure 5 present the distribution of the GSP values at baseline and EOT, as well as the change from baseline values. The distribution of the GSP values are highly skewed with a number of very large GSP values. The distribution of the change from baseline values also skewed, with many outliers, particularly highly negative values.

Figure 4 – Gravimetric Sweat Production at Baseline, EOT, and Change from Baseline to EOT in Study 301 (Observed Cases)



Veh=vehicle, SB=sofpironium bromide gel, BL=baseline, EOT=end of treatment
Source: Reviewer analysis using Applicant submitted datasets adgsp.xpt.

Figure 5 – Gravimetric Sweat Production at Baseline, EOT, and Change from Baseline to EOT in Study 302 (Observed Cases)



Veh=vehicle, SB=sofpironium bromide gel, BL=baseline, EOT=end of treatment
Source: Reviewer analysis using Applicant submitted datasets adgsp.xpt.

Missing Data Handling

The applicant conducted a tipping point analysis to evaluate the impact of missing data. For this analysis, multiple imputation was used to impute the change from baseline in GSP score (EOT-Baseline) for subjects with missing data. A shift parameter ranging from 0 to 90 units in GSP (delta) in steps of 5 units was added to the imputed value for SB gel subjects and subtracted from vehicle subjects (i.e., each treatment arm penalized towards 'no difference'). In Study 301, the analysis tipped ($p>0.05$), when 90 units were added to the subjects with missing data on the active arm and 90 units were subtracted from the subjects with missing data on the vehicle arm. In Study 302, the analysis tipped ($p>0.05$) when 15 units were added to the subjects with missing data on the active arm and 15 units were subtracted from the subjects with missing data on the vehicle arm. See Table 30. Because the analysis for change in GSP is mediated through the use of ranks, it is difficult to interpret the impact of the tipping point; however Study 302 tipped much sooner than Study 301.

Table 30 – Tipping Point Analysis for Ranked Change from Baseline in Gravimetric Sweat Production in Study 301 and 302 (ITT)

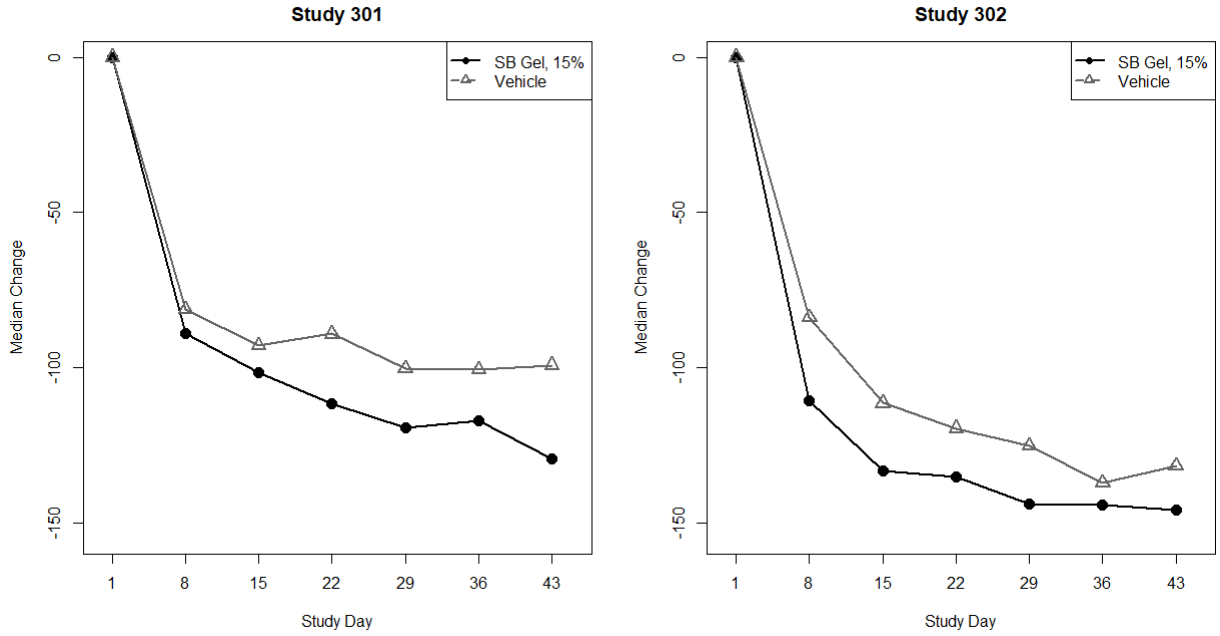
	Study 301		Study 302	
	SB Gel 15% (N=173) (%)	Vehicle (N=177) (%)	SB Gel 15% (N=180) (%)	Vehicle (N=171) (%)
Missing data	9.2	6.2	10.0	7.0
Shift parameter	P-value[1]		P-value[1]	
0	0.0019		0.0296	
5	0.0023		0.0368	
10	0.0028		0.0450	
15	0.0035		0.0544	
…	…			
85	0.0444			
90	0.0512			

[1] ANOVA on ranks adjusted for baseline and analysis center (multiple imputation)
Source: Clinical Study Report 301 (page 794) and Clinical Study Report 302 (page 801); findings reproduced by the statistical reviewer using adgspmi.xpt.

Efficacy over Time

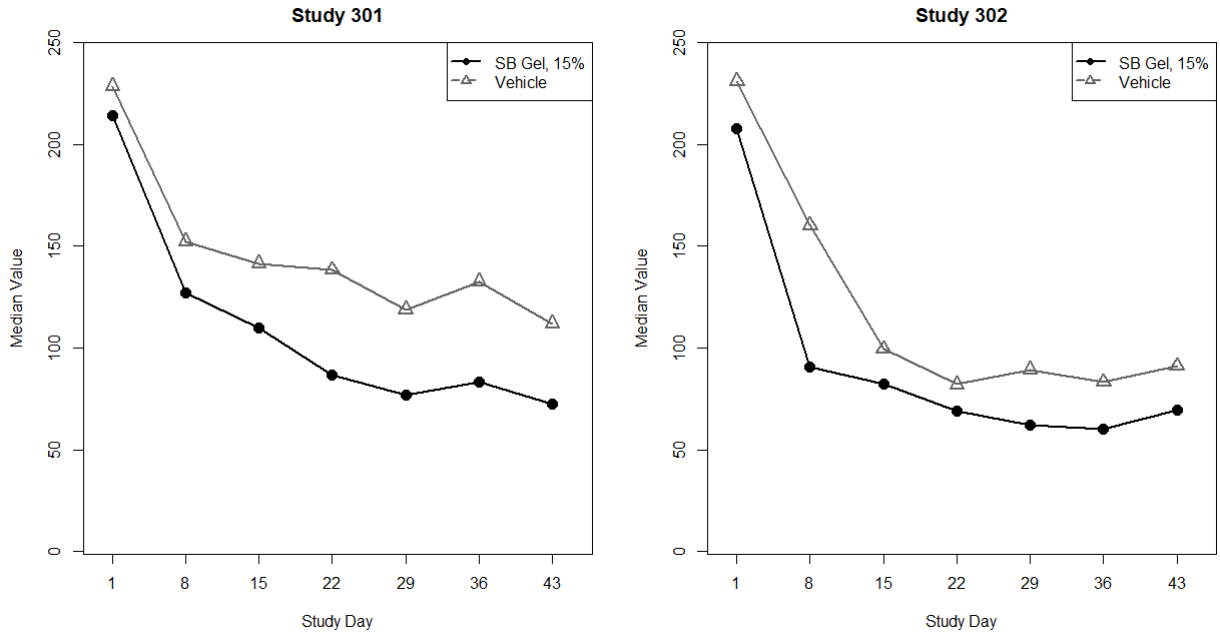
Figure 6 and Figure 7 present the median change from baseline GSP values by visit and median GSP values by visit, respectively. Subjects on both treatment arms experienced a large drop in GSP by Day 8, with smaller improvements later in the trial; however the decrease in GSP was consistently larger on the SB gel arm than the vehicle arm.

Figure 6 – Median Change from Baseline to End of Treatment in Gravimetric Sweat Production by Week in Studies 301 and 302 (Observed Cases)



Source: Reviewer analysis using Applicant submitted datasets adgsp.xpt.

Figure 7 – Median Value of Gravimetric Sweat Production by Week in Studies 301 and 302 (Observed Cases)

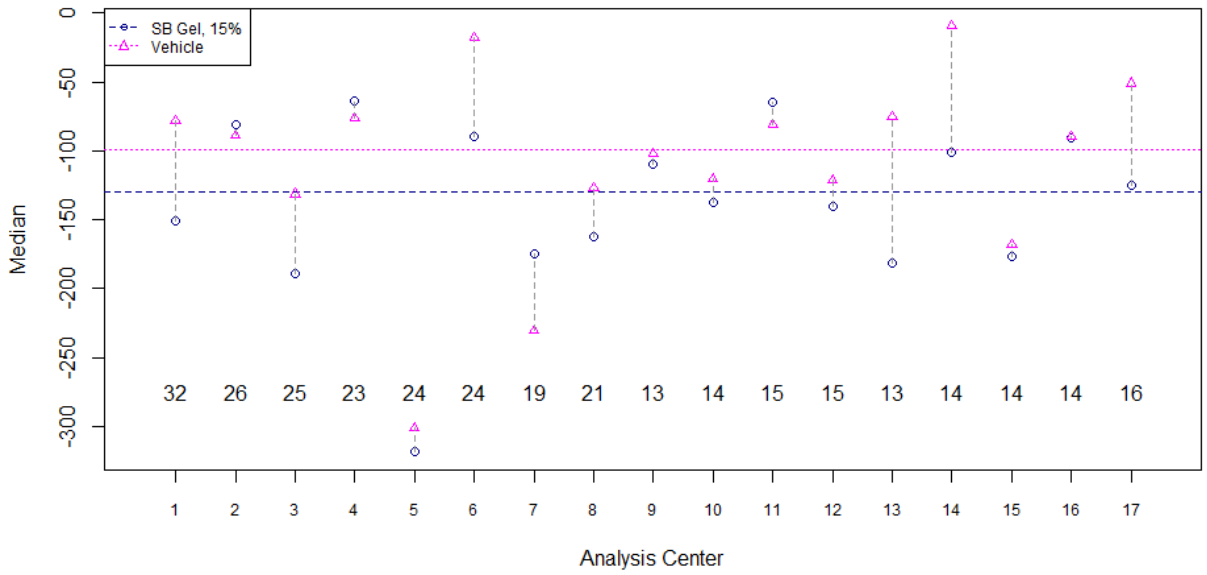


Source: Reviewer analysis using Applicant submitted datasets adgsp.xpt.

Efficacy by Center

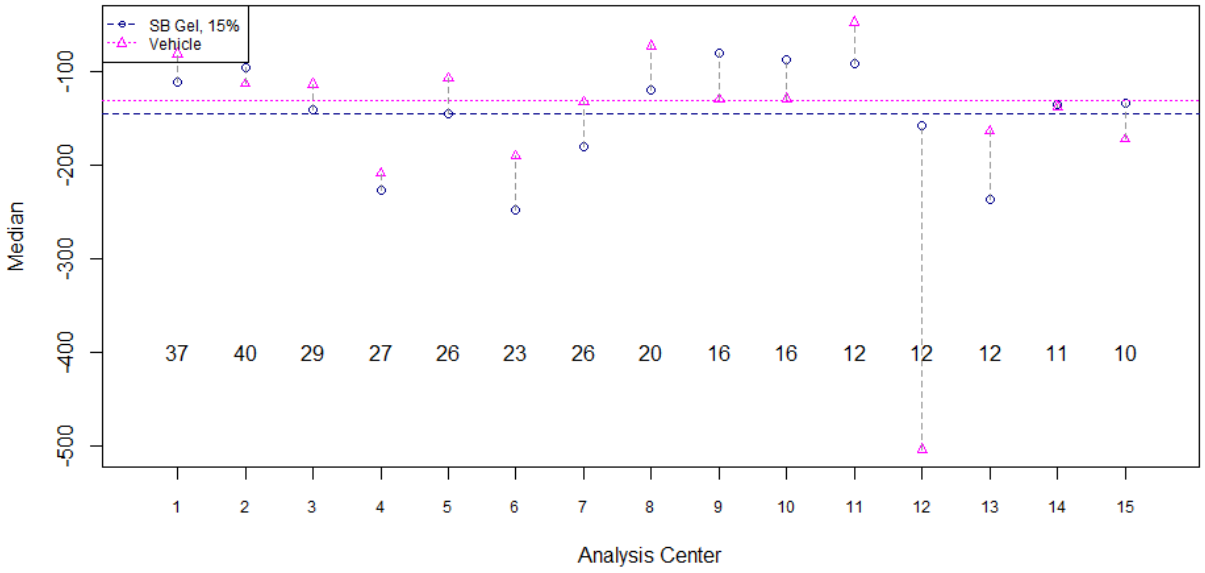
Study 301 randomized 350 subjects at 35 centers in the U.S. Study 302 randomized 351 subjects at 33 centers in the U.S. Many of the sites in both studies enrolled relatively few subjects. For the analysis, the protocol specified that small centers would be combined with larger center to create analysis center. For sites with <10 subjects, the lowest enrolling site was combined with the largest enrolling site, and then the second lowest enrolling site and the second largest enrolling site were combined, and so on. Median change in GSP by analysis center is presented in Figure 8 and Figure 9. Treatment effects were variable across analysis centers (particularly with Analysis Center 12 in Study 302), but most analysis centers had trends favoring SB gel over vehicle.

Figure 8 – Median Change in Gravimetric Sweat Production by Analysis Center in Study 301 (Observed Cases)



Numbers represent total number of subjects per analysis center
Source: Reviewer analysis using Applicant submitted datasets adgsp.xpt.

Figure 9 – Median Change in Gravimetric Sweat Production by Analysis Center in Study 302 (Observed Cases)



Numbers represent total number of subjects per analysis center
Source: Reviewer analysis using Applicant submitted datasets adgsp.xpt.

Findings in Subgroup Populations
Treatment effects across demographic subgroups were somewhat variable in the two studies, though the response rates for SB gel were generally larger than for vehicle in each subgroup, with the exception of the female subject subgroup. Note that this finding in sex subgroups is inconsistent with the subgroup analyses for the HDSM-Ax-7 scale response endpoint in which female subjects had a favorable treatment effect that was larger than that observed in male subjects. See Table 31 through Table 33.

Table 31 – Median Change in Gravimetric Sweat Production by Demographic Subgroups in Study 301 (ITT)

	SB Gel 15% (N=173)		Vehicle (N=177)	
	Median	25^{th}, 75^{th} %tile	Median	25^{th}, 75^{th} %tile
Age Group, (n_1, n_2)[1]				
10-17 years (15, 12)	-139.5	-170.3, -83.4	-95.4	-163.1, -68.5
≥18 years (158, 165)	-125.6	-204.2, -51.0	-102.5	-229.9, -25.5
Sex, (n_1, n_2)				
Female (98, 99)	-133.0	-190.8, -59.1	-138.6	-246.0, -55.7
Male (75, 78)	-124.1	-211.5, -48.0	-85.1	-174.5, -12.0
Race[2], (n_1, n_2)				
Black or African American (31, 43)	-98.8	-182.4, 20.3	-84.5	-228.8, 1.7

	SB Gel 15% (N=173)		Vehicle (N=177)	
White (140, 130)	-134.1	-207.1, -69.9	-105.5	-227.8, -40.4
Ethnicity, (n_1, n_2)				
Hispanic or Latino (61, 60)	-114.5	-162.8, -42.8	-106.4	-214.5, -35.5
Not Hispanic or Latino (111, 117)	-138.9	-206.5, -64.0	-99.5	-228.7, -21.7

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
[2] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
%tile = percentile
Medians and quartiles averaged over the 20 multiply imputed datasets
Note: the ITT population includes duplicate subject enrollments.
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt.

Table 32 – Median Change in Gravimetric Sweat Production by Demographic Subgroups in Study 302 (ITT)

	SB Gel 15% (N=180)		Vehicle (N=171)	
	Median	25th, 75th %tile	Median	25th, 75th %tile
Age Group, (n_1, n_2)[1]				
10-17 years (15, 10)	-140.7	-292.2, -45.1	-57.7	-135.5, -18.8
≥18 years (165, 161)	-143.5	-248.4, -77.0	-138.0	-235.3, -66.1
Sex, (n_1, n_2)				
Female (92, 103)	-115.5	-234.1, -71.0	-129.1	-249.7, -49.8
Male (88, 68)	-157.7	-303.4, -84.2	-144.1	-209.8, -71.1
Race[2], (n_1, n_2)				
Black or African American (32, 24)	-158.1	-318.0, -116.8	-133.0	-297.0, -38.9
White (141, 133)	-123.3	-234.3, -71.3	-134.9	-220.9, -65.0
Ethnicity, (n_1, n_2)				
Hispanic or Latino (48, 45)	-152.4	-320.7, -79.3	-126.4	-247.0, -66.1
Not Hispanic or Latino (132, 124)	-135.5	-243.2, -73.5	-133.9	-219.7, -54.5

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
[2] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
%tile = percentile
Medians and quartiles averaged over the 20 multiply imputed datasets
Note: the ITT population includes duplicate subject enrollments.
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt.

Table 33 – Median Change in Gravimetric Sweat Production by Demographic Subgroups in Pooled Studies 301 and 302 (ITT)

	SB Gel 15% (N=353)		Vehicle (N=348)	
	Median	25^{th}, 75^{th} %tile	Median	25^{th}, 75^{th} %tile
Age Group, (n_1, n_2)[1]				
10-17 years (30, 22)	-140.2	-265.8, -58.7	-91.5	-141.9, -23.4
≥18 years (323, 326)	-131.7	-218.7, -68.2	-125.6	-231.3, -48.1
Sex, (n_1, n_2)				
Female (190, 202)	-122.6	-204.7, -68.3	-133.1	-245.0, -51.8
Male (163, 146)	-145.0	-259.6, -65.4	-104.2	-204.6, -34.8
Race[2], (n_1, n_2)				
Black or African American (63, 77)	-136.3	-223.8, -55.6	-109.1	-231.7, -10.0
White (281, 263)	-131.6	-216.3, -71.3	-125.2	-225.1, -53.4
Ethnicity, (n_1, n_2)				
Hispanic or Latino (109, 105)	-125.4	-233.1, -58.3	-112.3	-232.2, -46.5
Not Hispanic or Latino (243, 241)	-138.8	-218.3, -71.0	-122.8	-224.6, -47.3

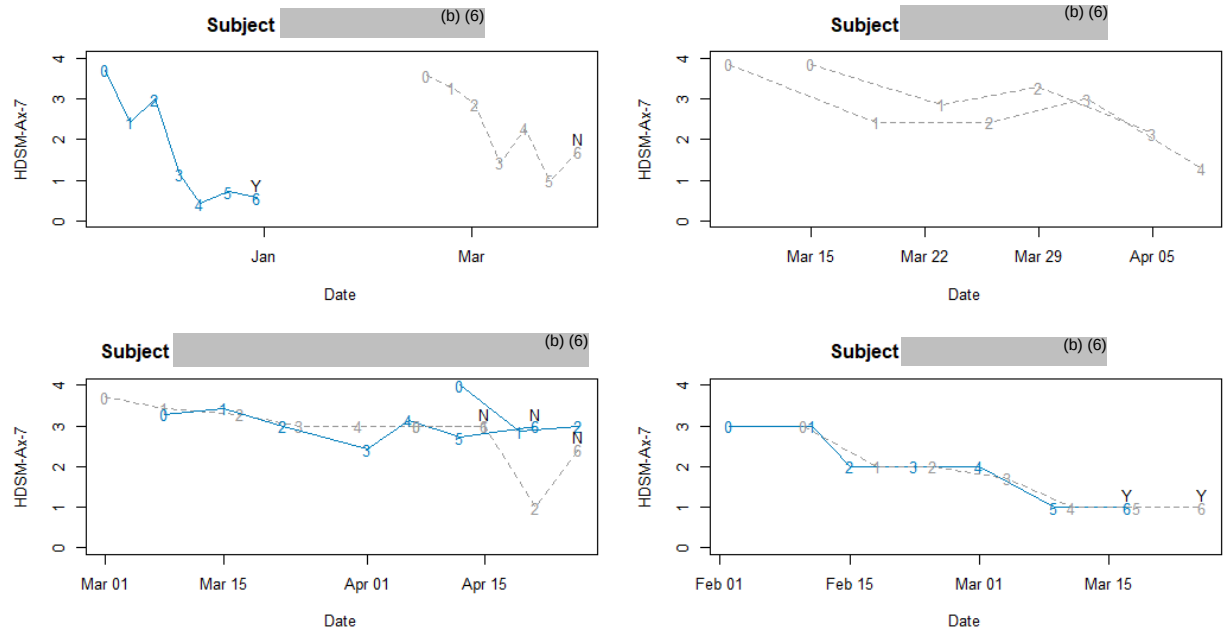
[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
[2] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
Note: the ITT population includes duplicate subject enrollments.
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt

Data Quality and Integrity

During the conduct of the studies, the Applicant identified 5 subjects who enrolled multiple times in either Study 301 or Study 302. The issue was identified when a subject enrolled in one study returned study treatment labeled for the other study at a study visit. Data review identified additional subjects through demographic matching. Three subjects were randomized twice at different centers, 1 subject was randomized 4 times and was screen-failed once, and 1 subject was randomized once and screen-failed once. Thus, of these 5 subjects, 4 subjects were randomized a total of 10 times. The applicant maintained the definition of the ITT population as all randomized subjects and defined the mITT population to exclude these 4 subjects from all analyses (the 5^{th} subject who was only randomized once is included in the mITT population). One subject completed all visits at one center before they enrolled in the other center; however the other 3 subjects had overlapping enrollments at multiple sites. Figure 10 presents the HDSM-Ax-7 scale scores by calendar day for these 4 subjects, overlapping the data from the separate enrollments. For the 3 subjects with coincident enrollments, the HDSM-Ax-7 scale scores recorded on similar calendar days at the different centers were generally similar, with a few exceptions. The figure also notes whether the subject was classified as a HDSM-Ax-7 responder at EOT for a particular enrollment. If no letter is noted, the subject was treated as

having missing data. As noted above, the results from the ITT and mITT analyses were very similar for the co-primary endpoints, and the multiple enrollments did not have any impact on the conclusions.

Figure 10 – HDSM-Ax-7 Scale Scores by Date for Subjects with Multiple Enrollments in Studies 301 or 302.



Note: Blue solid lines represent randomizations to SB gel and gray dashed lines represent randomizations to vehicle. Numerals 0 through 6 represent the Study Week of the assessment, where 6 may represent either Week 6 or EOT. For subjects with a EOT visit, Y represents a subject classified as a responder, and N represents a subject classified as a non-responder (≥2 point improvement in the HDSM-Ax-7 scale score). Enrollments without a Y or N noted were handled as missing data.
Source: Reviewer analysis using Applicant submitted datasets adhdsm.xpt.

Efficacy Results – Secondary and other relevant endpoints

The protocol defined three secondary endpoints: ≥1 point improvement in the HDSM-Ax-7 scale score, ≥2 point improvement in the HDSM-Ax-7 scale score and ≥70% reduction in GSP, and ≥1 point improvement in the HDSM-Ax-7 scale score and ≥50% reduction in GSP. The three endpoints were analyzed sequentially. The secondary endpoints are closely related to the co-primary endpoints, and all three were statistically significant in each study. See Table 34.

Table 34 – Secondary Endpoint Results at EOT in Studies 301 and 302 (ITT)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
≥1 point improvement in HDSM-Ax-7 Scale Score				
Estimated proportion (adjusted[1]) (%)	82.8	69.5	89.9	80.8
p-value		0.0053		0.0165
≥2 point improvement in HDSM-Ax-7 Scale Score and **≥70%** reduction in GSP				
Estimated proportion (adjusted[1]) (%)	32.1	10.2	35.5	21.4
p-value		<0.0001		0.0059
≥1 point improvement in HDSM-Ax-7 Scale Score and **≥50%** reduction in GSP				
Estimated proportion (adjusted[1]) (%)	54.3	33.3	68.7	54.6
p-value		0.0004		0.0139

[1] Estimates from logistic regression adjusted for baseline and analysis center.
Source: Clinical Study Report 301 (page 77-79) and Clinical Study Report 302 (page 79-81); findings reproduced by the statistical reviewer using adhdsmi.xpt and adrespmi.xpt.

8.1.3. Assessment of Efficacy Across Trials

Dose/Dose Response

Study BBI-4000-CL-203 was a phase 2 dose response study that evaluated SB gel 5%, 10%, and 15% versus vehicle. The study randomized 227 subjects. Efficacy was assessed as ≥1 grade improvement on the HDSM-Ax-11 scale score (using 11 question responses). The proportion of subjects achieving this endpoint was 75.9%, 78.9%, 70.2%, and 54.4% for SB gel 15%, 10%, 5%, and vehicle, respectively. The applicant selected the 15% dose for phase 3 development.

Efficacy Results for Studies BBI-4000-CL-301 and BBI-4000-CL-302

The co-primary efficacy endpoints in Studies 301 and 302 were the proportion of subjects with ≥2 point improvement in HDSM-Ax-7 from baseline to EOT and the change from baseline in GSP from baseline to EOT. Both endpoints were statistically significant in each study based on the protocol-specified primary analysis. Change in GSP was analyzed using ranks because of the skewness of the distribution.

Because different versions of the HDSM-Ax scale were used for children ≥9 to <12 years of age and adolescents and adults ≥12 years of age, the recommended presentation of results is to use the analysis including subjects ≥12 years of age, as it would not be appropriate to combine the results from both instruments. Across the two studies, only 5 subjects <12 years of age were enrolled. For the change in GSP endpoint, while using a ranked analysis minimizes the impact of the skewness of the distribution on the analysis, estimates based on the difference in ranks are not clinically meaningful. Medians and the quartiles (25th and 75th percentiles) for the unranked

data are more useful for presenting the magnitude of the treatment effect. See Table 35.

Table 35 – Co-primary Efficacy Results in Studies 301 and 302 (ITT)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
≥2 point improvement in HDSM-Ax-7 **(≥12** years)	N=172	N=177	N=178	N=169
Estimated proportion (adjusted[1]) (%)	48.8	29.3	64.2	47.7
p-value	0.0005		0.0040	
Estimated proportion (unadjusted[2]) (%)	50.4	32.1	63.3	47.1
Treatment difference (95% CI)	18.3 (8.0, 28.7)		16.2 (5.4, 26.9)	
Change from Baseline[3] in GSP	N=173	N=177	N=180	N=171
Difference in Ranks[4]				
LS Means [Ranks] (SE)	-14.9 (6.8)	14.8 (6.7)	-9.9 (7.1)	11.8 (7.5)
p-value	0.0019		0.0296	
Values[5]				
Median	-127.8	-100.3	-142.6	-134.2
25th percentile, 75th percentile	-200.5, -52.4	-227.5, -28.5	-260.1, -75.0	-230.0, -59.5

[1] Estimates and p-value from logistic regression adjusted for baseline and analysis center (multiple imputation).
[2] Estimates and CI using Wald method (multiple imputation)
[3] Baseline value calculated from the median GSP value from Visits 2, 3, and 4; EOT value calculated from the median GSP value from Visits 10, 11, and 12.
[4] ANOVA on the difference in ranks adjusted for baseline rank and analysis center (multiple imputation).
[5] Medians and quartiles averaged over the 20 multiply imputed datasets.
CI= confidence interval; LS=Least squares; SE= standard error
Source: Clinical Study Report 301 (page 62, 173) and Clinical Study Report 302 (page 64, 180); findings reproduced or conducted by the statistical reviewer using adhdsmi.xpt and adgspmi.xpt.

Subgroup Findings

Treatment effects across demographic subgroups were generally in favor of SB gel relative to vehicle for both endpoints for the combined studies. Among subgroups with at least a moderate sample size, the only subgroup in which the vehicle had a more favorable outcome was for the change in GSP endpoint for female subjects. Note that this finding is inconsistent with the subgroup analyses for the HDSM-Ax-7 response endpoint in which female subjects had a favorable treatment effect that was larger than that observed in male subjects. The reason for this inconsistency across endpoints is unclear. See Table 36 and Table 37.

Table 36 - Percentage of Subjects with **≥2** point improvement in HDSM-Ax-7 by Demographic Subgroups in Pooled Studies 301 and 302 (ITT)

	SB Gel 15% (N=353)	Vehicle (N=348)	Difference (95% CI)
Age Group, (n_1, n_2)[1] (%)			
[redacted] (b) (4)			
12-17 years (27, 20)	55.4	32.5	22.9 (-5.9, 51.6)
≥18 years (323, 326)	57.1	39.9	17.2 (9.5, 24.9)
Sex, (n_1, n_2) (%)			
Female (190, 202)	62.1	38.8	23.3 (13.4, 33.1)
Male (163, 146)	51.1	39.7	11.4 (0.2, 22.6)
Race[3], (n_1, n_2) (%)			
Black or African American (63, 77)	51.0	33.2	17.8 (1.5, 34.1)
White (281, 263)	59.2	41.8	17.4 (8.9, 25.9)
Ethnicity, (n_1, n_2) (%)			
Hispanic or Latino (109, 105)	55.3	42.3	13.0 (-0.4, 26.4)
Not Hispanic or Latino (243, 241)	57.7	37.9	19.7 (10.8, 28.7)

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.
[redacted] (b) (4)

[3] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
NA= not available; sample size too small for meaningful calculations
Source: Reviewer analysis using Applicant submitted datasets adhdsmi.xpt and adsl.xpt

Table 37 - Median Change in Gravimetric Sweat Production by Demographic Subgroups in Pooled Studies 301 and 302 (ITT)

	SB Gel 15% (N=353)		Vehicle (N=348)	
	Median	25^{th}, 75^{th} %tile	Median	25^{th}, 75^{th} %tile
Age Group, (n_1, n_2)[1]				
10-17 years (30, 22)	-140.2	-265.8, -58.7	-91.5	-141.9, -23.4
≥18 years (323, 326)	-131.7	-218.7, -68.2	-125.6	-231.3, -48.1
Sex, (n_1, n_2)				
Female (190, 202)	-122.6	-204.7, -68.3	-133.1	-245.0, -51.8
Male (163, 146)	-145.0	-259.6, -65.4	-104.2	-204.6, -34.8
Race[2], (n_1, n_2)				
Black or African American (63, 77)	-136.3	-223.8, -55.6	-109.1	-231.7, -10.0
White (281, 263)	-131.6	-216.3, -71.3	-125.2	-225.1, -53.4
Ethnicity, (n_1, n_2)				
Hispanic or Latino (109, 105)	-125.4	-233.1, -58.3	-112.3	-232.2, -46.5
Not Hispanic or Latino (243, 241)	-138.8	-218.3, -71.0	-122.8	-224.6, -47.3

[1] (n_1, n_2) represents the sample size for SB gel 15% and vehicle, respectively.

[2] Predominant race if multiple races selected. Race groups with 5 or fewer subjects per treatment arm not shown.
Source: Reviewer analysis using Applicant submitted datasets adgspmi.xpt, and adsl.xpt

Additional Efficacy Considerations

Review of COAs for Evaluation of Clinical Benefit

The FDA reviewed the Applicant's COA evidence dossier for the two versions of the HDSM-Ax instrument (i.e., Adult and Child versions). The two instrument versions were reviewed for content validity and other measurement properties (reliability, construct validity, responsiveness), as well as score interpretability.

Content Validity

The applicant completed the following instrument development activities to evaluate the content validity of the HDSM-Ax – Adult and Child Versions:

- Literature review
- Expert input (clinician interviews)
- Patient input (hybrid concept elicitation and cognitive interviews in adults; cognitive interviews in adolescents)

The review team evaluated the data generated from these instrument development activities. Both literature and patient input confirmed that the content of the HDSM-Ax instrument assess important and relevant aspects of excessive underarm sweating. In general, the HDSM-Ax instrument was well-understood and interpreted as intended in adolescents (12 -17 years) and adults. However, during the preliminary evaluation of content validity there was comprehension issues identified in younger children when completing the HDSM-Ax instrument, specifically related to certain item stems (questions) and response options. As such, the Applicant created two versions of the HDSM-Ax instrument, the HDSM-Ax – Adult Version (for participants ≥ 12 years of age) and – Child Version (for participants 9 to 11 years of age). Further review of both HDSM-Ax versions identified concerns related to content validity and/or recall period selection that are summarized below:

HDSM-Ax-7 – Adult Version

- The HDSM-Ax-7 recall period ("since you woke up yesterday") does not capture a complete picture of the condition since it is only measuring the patient's sweating experience the day before the clinic visit. Based on the qualitative data, the patient experience of excessive underarm sweating may vary from day-to-day depending on the activities for that day.

Reviewer comment: The Applicant was advised in the IND stage to administer the HDSM-Ax as a daily diary in the evening to minimize recall error. However, the Applicant elected not to modify the recall period.

HDSM-Ax-7 – Child Version

- Insufficient qualitative evidence to support the content validity of the HDSM-Ax-7 scale for participants aged 9-11 years with axillary hyperhidrosis. The HDSM-Ax-7 – Child Version was only cognitively debriefed in three participants who experienced axillary involvement. As such, it is difficult to determine whether the instrument is relevant and well-understood by this age subgroup.
- The HDSM-Ax-7 recall period has limitations, which are described above in the HDSM-Ax – Adult Version.

Reviewer comment: This review team notes that modifications were made to the HDSM-Ax to make it age-appropriate (e.g., use of age-relevant vocabulary) to ensure language comprehension and comprehension of the target concept. However, some of these modifications have altered the measurement concepts and attributes, despite the Applicant's claim that the same items and measurement concepts are used from the Adult Version. For example,

- There are items in the HDSM-Ax – Adult Version that measures underarm sweat severity ("Since you woke up yesterday, how severe…?); however, these items in the HDSM-Ax –Child version are now measuring the amount of underarm sweat ("Since you woke up yesterday, how much…?").
- There is an item in the HDSM-Ax –Adult Version that measures underarm sweating when "nervous, stressed, or anxious," which has been changed to "nervous, scared, or worried" in the HDSM-Ax –Child Version. This reviewer notes the similarity of these concepts, however, in addition to the change in attribute (severity to amount) these items are no longer the same.
- There is an item in the HDSM-Ax –Adult Version that measures underarm sweating "after little or no physical exercise," which has been changed to "after sitting quietly" in the HDSM-Ax –Child Version. Again, the change in measurement concept and attribute no longer makes these items comparable.

Refer to the full COA review by Sarah Stothers, RN, MSN, MPH, the Division of Clinical Outcome Assessment (DCOA) for detailed results of the content validity of these COAs.

<u>Other Measurement Properties (Reliability, Construct validity, Responsiveness)</u>

The Applicant evaluated the other measurement properties of the HDSM-Ax using data from three studies:

- Study BBI-4000-CL-201 (n=189): A Multicenter, Randomized, Double Blind, Vehicle-Controlled Study to Evaluate the Safety and the Effect on Sweat Production of 3 Concentrations of Topically Applied BBI-4000 Gel in Subjects with Axillary Hyperhidrosis.

- Study BBI-4000-CL-301 (n= 349)
- Study BBI-4000-CL-302 (n= 347)

Initially, the Applicant combined the data from to conduct the psychometric analyses in Studies BBI-4000-CL-301 and -302. However, due to the differences in the instruments as stated above in the content validity subsection, the data cannot be adequately pooled. Further, there were no participants aged 9-11 years enrolled in Study BBI-4000-CL-203 and limited participants in this age subgroup enrolled in Studies BBI-4000-CL-301 and -302 (n = 5) which made the data for the HDSM-Ax – Child Version uninterpretable. Therefore, the review team focused on the psychometric findings for the HDSM-Ax – Adult Version, specifically the HDSM-Ax-7 scale score, from Studies BBI-4000-CL-301 and -302 since these were the studies reported in the COA evidence dossier.

The analysis population for the HDSM-Ax- – Adult Version was comprised of participants ≥12 years and referred to as the "reduced sample." The psychometric properties for the HDSM-Ax-7 scale score were generated from three timepoints including Baseline, Day 15, and Day 43 (missing data for the HDSM-Ax-7 scale score or any of the supplementary assessments were not imputed).

Based on the review team's assessment of the other measurement properties, results from the assessment of construct validity (convergent validity, divergent validity, and known groups validity) and responsiveness were generally within an acceptable and reasonable range. However, there was limited data to support reliability. Specifically, the results from the test-retest reliability assessment were conflicting depending on the analysis population definition.

Refer to the full COA review by Sarah Stothers, RN, MSN, MPH, the Division of Clinical Outcome Assessment (DCOA) for detailed results of the other measurement properties of this COA.

Score Interpretability

The Applicant performed anchor-based analyses using data from Studies BBI-4000-CL-301 and -302 to derive a meaningful within-patient score change threshold in the HDSM-Ax-7 scale score from the HDSM-Ax - – Adult Version[1].

The Applicant proposed a 2-point reduction (improvement) in the HDSM-Ax-7 scale score from baseline to Day 43 (EOT) to represent a clinically meaningful within-patient score change. Based on the SPA correspondence dated January 18, 2019 (DARRTS Reference ID: 4378287) during the IND phase, the Agency agreed to the Applicant's proposal of at least a 2-point improvement in the HDSM-Ax-7 scale score (on a 0-4 score). A 1-point meaningful within-patient change

[1] Interpretation of meaningful within-patient change for the HDSM-Ax-7 Child Version was uninterpretable due to Insufficient sample size to conduct anchor-based analyses.

threshold for the HDSM-Ax-7 scale score was not considered interpretable due to insufficient evidence.

Refer to the full COA review by Sarah Stothers, RN, MSN, MPH, the Division of Clinical Outcome Assessment (DCOA) for detailed results of score interpretability of this COA.

Conclusion

The HDSM-Ax-7 scale score from the HDSM-Ax – Adult Version and the corresponding responder analysis endpoints that use a 2-point responder threshold could potentially support labeling claims related to improvement in excessive underarm sweating in patients 12 years of age and older, if also supported by the clinical trial study design and statistical analysis (e.g., separate endpoint from the HDSM-Ax-7 scale score from the HDSM-Ax – Child Version).

(b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical development program consisted of 9 studies (six phase 2 studies and three phase 3 studies) in which subjects were treated with sofpironium bromide, 643 of whom were treated at the 15% dose intended for marketing, 118 of whom were treated for at least 48 weeks. The development program used three formulations of sofpironium bromide gel; six studies enrolled subjects with primary axillary hyperhidrosis who were treated with the intended commercial formulation (isopropyl myristate [IPM1]). The safety review focuses on sofpironium gel IPM1 formulation trials and studies to provide data for labeling.

BBI-4000-CL-301 (301) and BBI-4000-CL-302 (302) were the phase 3, pivotal trials conducted using the to-be-marketed sofpironium gel 15% formulation. BBI-4000-CL-303 (303) was an open-label (OL), 52-week, long-term study in adults (SB 5% and 15%). This study enrolled treatment-naïve subjects who were not enrolled in trials 301 or 302.

Five additional studies were conducted during which subjects were exposed to sofpironium bromide (SB) gel 15% IPM1 formulation.

- BBI-4000-CL-102: phase 1, PK study
- BBI 4000-CL-105: OL Sofpironium Bromide Gel, 15%, children and adolescents, ≥ 9 to <17 Years of Age
- BBI-4000-CL-108: OL, long-term study in children and adolescents ≥ 9 years to < 17 years (from Study 105)
- BBI-4000-03: Randomized, double-blind, repeat dose (SB 0%, 5%, 10%, 15%)

- BBI-4000-05: OL, 14-day, repeat dose, SB 15%, two formulations (IPM1 and IPM2)

During the course of the studies, five subjects were identified as enrolling at more than one site in one study, or in both studies 301 and 302. The five subjects were enrolled/counted as nine subjects; for safety, they were classified as duplicate subjects and noted in the individual study subject listings.

The Applicant provided definitions for the following populations:

- The Safety population was all subjects randomized in the study who received study drug, either vehicle or sofpironium bromide, 15%, at least once.
- The Intent-to-treat (ITT) population included all subjects randomized, including subjects with duplicate enrollments either within (301), or across (301) and (302).
- The modified intent-to-treat (mITT) population was a subset of the ITT population that excluded subjects with duplicate enrollments either within (301), or across (301) and (302).
- The per-protocol (PP) population was a subset of the mITT population, consisting of subjects who met specific criteria:

1. Met all inclusion/exclusion criteria
2. Had not taken or applied any interfering concomitant medications
3. Completed visits and collected data as specified

The subjects with duplicate enrollments were retained and the safety events included in the analyses. The Applicant analyzed the data using the ITT population or safety population.

- duplicate subjects with repeat registrations in the same study had each registration analyzed as a different study subject with his/her unique subject identifier
- duplicate subjects who registered in both BBI-4000-CL-301 and BBI-4000-CL-302, had registrations remain as they were for each of the respective studies.

Subject safety data were analyzed according to the treatment received.

This safety review will focus on the primary safety data; phase 3 pivotal trials 301 and 302 were the focus of the Applicant's safety analyses. Additionally, discussion in this safety review pertains to the pivotal trials unless otherwise specified, with the following exceptions: deaths, serious adverse events, and pregnancies. Generally, the safety review will only discuss comparisons between the sofpironium bromide 15% and vehicle groups in the Phase 3 studies.

8.2.2. Review of the Safety Database

Overall Exposure
Overall, the safety of sofpironium bromide gel has been evaluated in 21 completed clinical studies in subjects ≥ 9 years of age. The Applicant states that 1721 subjects have been exposed to sofpironium bromide drug substance at any formulation and concentration (age 13 years-72 years).

There were three SB formulations evaluated during the SB drug development program for the axillary hyperhidrosis indication. The Applicant developed and identified IPM1 as the formulation intended for to-be-marketed use and the PAH indication.
The clinical experience with IPM1 formulation, sofpironium bromide gel, 15% was as follows:

- Studies in healthy subjects (Studies BBI-4000-CL-103, and BBI-4000-CL-109).
- One Phase 2 vehicle-controlled, randomized, multidose, double-blind study in subjects with primary axillary hyperhidrosis (Study BBI-4000-CL-203).
- Two identical pivotal Phase 3 trials (Studies BBI-4000-CL-301, Studies BBI-4000-CL-302).
- Six OL studies in subjects with primary axillary hyperhidrosis (BBI-4000-CL-303, BBI 4000-CL-105, BBI-4000-CL-108, BBI-4000-CL-102 [maximum use], BBI-4000-03, and BBI-4000-05).

Overall, 643 subjects were exposed to the IPM1 formulation which is the intended commercial formulation. For long-term exposure, 118 subjects were exposed for at least 48 weeks. Note that since pediatric subjects from OL study BBI-4000-CL-105 were subsequently enrolled in long-term, OL study BBI-4000-CL-108, these 21 subjects were counted once.

Table 38: Safety Population, Size and Denominators

Safety Database for the Study Drug, IPM1 [1] Individuals exposed to the study drug in this development program for the indication under review N=643 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug SB 15% (n= 643)		Placebo (n=347)
Controlled trials conducted for this indication[2]	353		347
All other than controlled trials conducted for this indication[3]	290		
Controlled trials conducted for other indications[4]	0		0

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Regarding the pediatric population, exposure for patients of age 9 years to ≤ 12 years appears low in number. During clinical trials 301 and 302, no subject was exposed who was age 9 years. For ages 10 and 11 years, 2 of the 5 enrolled subjects with PAH were exposed during clinical trials 301 and 302. For the demographics, see Table XX. Twenty-one pediatric subjects were exposed during OL studies.

Adequacy of the safety database:

Overall, over 1700 subjects were exposed to the drug substance, and 643 subjects were exposed to the to-be-marketed IPM1 formulation, with over 100 exposed for almost one year. The exposure appears adequate to inform safety for the primary axillary hyperhidrosis indication for ages 12 years and older.

For the pivotal phase 3 clinical trials, five subjects were enrolled for age 9 to 11 years, and two received study drug. Due to the underlying etiology, PAH is considered the same disease in the pediatric population as in adults; therefore, the Agency is allowing for consideration of safety data in adolescents and adults for this indication without requesting additional studies in 9- to 11-year-old patients.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Reasonably applicable clinical evaluations were conducted to assess the safety of sofpironium bromide gel, and those evaluations were generally performed at appropriate time(s) during the trial(s). However, see Section 4.1 regarding concerns regarding study conduct and data reliability. Those concerns largely pertained to timing of assessments, and they did not affect trial efficacy or safety. The OSI audit did not raise specific concerns regarding the safety data.

Categorization of Adverse Events

Treatment-emergent adverse events (TEAE) were events of onset during or after the first dose of study drug administration, or existing events which worsened after the initial study drug dose.

The Applicant further differentiated and collected by specific categories: severe TEAEs; TEAEs of special interest; anticholinergic TEAEs; local reaction site TEAEs. TEAEs were summarized by treatment group and severity. The Verbatim terms on electronic case report forms (eCRFs) were mapped to preferred terms and system organ classes using Version 23.1 of MedDRA.

The Applicant collected Serious adverse events (SAEs), TEAEs leading to discontinuation from the study, TEAEs of special interest, and anticholinergic TEAEs. Additional analyses were conducted of TEAEs leading to dose interruption and any related serious TEAEs.

TEAEs of special interest (or AESIs) were events considered related to sofpironium bromide (SB) anticholinergic activity. The AESIs pre-specified were:

- Blurred vision
- Mydriasis (bilateral and unilateral)
- Urinary hesitation

Routine Clinical Tests

For Study 301 and 302, the routine clinical assessments were vital signs, clinical laboratory assessments chemistry and hematology, urine pregnancy testing.

- Vital sign measurements were systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature. Vital signs were collected at Baseline, Day 1, Visits 5, 6, 7, 8, 9, 12 and 13.
- The clinical laboratory assessments scheduled for Screening and Visit 12 (Day 43) were hematology panel including differential, chemistry to include basic metabolic panel and liver function tests, and routine urinalysis. Clinical laboratory assessments were

collected at Screening and Visit 12 (Day 43).

- Urine pregnancy testing in subjects of childbearing potential were collected at Screening and Visits 4, 8 and 12. The tests were provided by the Sponsor.

8.2.4. Safety Results

Deaths

No deaths were reported for Studies BBI-4000-CL-301 and BBI-4000-CL-302.

One death was reported in the BBI 4000 CL 303 long-term, multicenter (US), randomized, open-label, long-term safety study of sofpironium bromide gel, 5% and 15% in subjects with axillary hyperhidrosis. Subject (b) (6) was a 57-year-old African American male who had received sofpironium 5% gel, 285 doses (40 weeks, 5 days). He died of septic shock secondary to pneumonia. The investigator concluded that the fatal event was unrelated to study drug. The Agency sent an IR to the Applicant for additional information; the death certificate also stated that the subject had AIDS, which was unknown to the investigator.

Reviewer comment: It is unlikely that the pneumonia and septic shock events were related to IP, and more likely related to the undisclosed AIDS diagnosis, though the condition was of unknown duration. The deceased subject was exposed to the 5% dose of IP; therefore, no conclusions can be made regarding the 15% strength of IP.

Serious Adverse Events

For Study 301, one serious adverse event (SAE) was reported.
Subject (b) (6) was a 45-year-old Black male, with a history of axillary hyperhidrosis and chemical allergy, food allergy, drug hypersensitivity to Keflex, famotidine, and loratadine, hand contact dermatitis, and anemia. His concomitant medications were topical triamcinolone for dermatitis and Arm and Hammer Deodorant. The subject was randomized to sofpironium gel group and completed treatment and application of IP through Day 43. During the study, the subject reported TEAEs graded as mild: hematocrit decreased; hemoglobin decreased; mean cell hemoglobin concentration decreased (2 events); mean cell volume decreased; COVID-19. On Day 61 during the follow up period, the subject presented to the emergency department with diffuse abdominal pain of one week duration. Computed tomography (CT) of the abdomen and pelvis reportedly suggested peritonitis with pelvic free fluid and fluid in the right lower quadrant, and diffuse small bowel dilatation. He was hospitalized for treatment including nasogastric tube for bowel decompression and drainage catheter placement to alleviate pelvic/perirectal fluid collection. Hospital medications were folic acid, paracetamol, and famotidine. The small bowel obstruction was considered resolved on Day 75. He completed the study on Day 98. The investigator considered the AE serious and not related to study treatment.

Reviewer Comment: The small bowel obstruction event symptoms began 11 days after the last application of IP. Ileus and bowel symptoms are known adverse events which can be related to anticholinergic medications; however, the half-life of sofpironium is brief and unlikely to be present at the time of symptom onset. Therefore, it is unlikely that the serious AE was related to IP application.

For Study 302, one SAE was reported.
Subject (b) (6) was a 23-year-old white female with a history of axillary hyperhidrosis, neck and back pain. Her concomitant medications were: levonorgestrel; cannabinoids (respiratory); meloxicam; cyclobenzaprine for neck/back pain; cyanobalamin; Old Spice Deodorant; Arm and Hammer Deodorant. She was randomized to the IP arm. On Day 11, the subject was diagnosed with appendicitis, which was confirmed by computed tomography (CT) of the abdomen and pelvis. An appendectomy was performed laparoscopically, with treatment intravenously with ceftriaxone, metronidazole, morphine, ondansetron. The subject was discharged on Day 12 with oral tramadol and amoxicillin for post-op prophylaxis. Study drug was restarted on Day 13, applied through Day 44, and the study was completed on Day 58. The investigator considered the appendicitis AE serious and not related to study drug application.

Reviewer comment: The appendicitis event was serious requiring surgical intervention, and occurred after exposure to IP. Though not likely, it is possible that the SAE was related to IP as the SAE was temporally related to IP administration.

Dropouts and/or Discontinuations Due to Adverse Effects

For Study 301, five subjects reported discontinuation due to eight TEAE events. The AEs as reported (#subjects) were: vision blurred (1); application site dermatitis, bilateral (2); urinary retention (1); mydriasis (1); dry mouth (1); application site pain, bilateral (2).

For Study 302, nine subjects reported discontinuation due to 14 TEAEs. The AEs as reported (#subjects) were: vision blurred (2); mydriasis (4); application site dermatitis (3); application site pain (1); application site erythema (1); dry eye (1); dry mouth (2).

No vehicle group subjects discontinued the studies due to an AE.

Reviewer comment: The reported AEs leading to study discontinuation were consistent with anticholinergic effects (vision blurred, urinary retention, mydriasis, dry mouth, dry eye), likely related to study drug use. Local skin reactions (LSR) were also reported, including application site pain, dermatitis, or erythema. LSRs are reported commonly with topical therapeutics, were not serious in severity, and reversible upon discontinuation. The anticholinergic effects and LSR can be addressed in labeling.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant defined treatment emergent adverse events (TEAEs) as AEs with onset during or after first dose of study drug, and current events that became worse after the first IP dose during the study.

Investigators reported AEs by verbatim terms which were mapped to preferred terms and system organ classes using Version 23.1 of MedDRA. AEs were recorded on electronic case report forms (eCRFs). TEAEs were summarized by treatment group (IP and vehicle) and severity.

No serious treatment emergent AEs or deaths were reported. The TEAEs reported numbered similarly for Study 301 compared to Study 302. TEAEs were reported more commonly in the IP arm compared to the vehicle group, including any TEAEs and severe TEAEs. TEAEs leading to dose modification, drug discontinuation, and permanent discontinuations from the study were only reported in those treated with SB gel. See Table 28.

Table 39: Number of Subjects reporting TEAEs, Safety Population

	Trial 301		Trial 302		Total	
	SB 15% N=173 n (%)	Vehicle N=176 n (%)	SB 15% N=180 n (%)	Vehicle N=171 n (%)	SB 15% N=353 n (%)	Vehicle N=347 n (%)
At least (1)TEAE	62 (35.8)	23 (13.1)	81 (45.0)	23 (13.5)	143 (40.5)	46 (13.3)
Serious TEAE	1 (0.6)	-	1 (0.6)	-	2 (0.6)	-
Treatment-related (TR) serious TEAE	-	-	-	-	-	-
Severe TEAE	4 (2.3)	-	5 (2.8)	-	9 (2.5)	-
Any TR TEAE	51 (29.5)	9 (5.1)	63 (35.0)	9 (5.3)	114 (32.3)	18 (5.2)

Source: Adapted from Table 4.1.1.1

The TEAEs reported more frequently for the SB 15% group compared to vehicle were those which were considered anticholinergic.

Table 40: Summary of Treatment-Emergent Adverse Events >1%, by Subject

	Trial 301		Trial 302		Total	
System organ class	SB gel 15% N=173 n (%)	Vehicle N=176 n (%)	SB gel 15% N=180 n (%)	Vehicle N=171 n (%)	SB gel 15% N=353 n(%)	Vehicle N=347 n(%)
Infections	6 (3.5)	2 (1.1)	20 (11.1)	5 (2.9)	26(7.4)	7 (2.0)
COVID-19 Inf	4 (2.3)	2 (1.1)	4 (2.2)	-	8 (2.3)	2 (0.6)
Nervous System	2 (1.1)	3 (1.7)	6 (3.3)	-	8 (2.3)	3 (0.9)
Headache	2 (1.2)	3 (1.7)	4 (2.2)	-	6 (1.7)	3 (0.9)
Eye Disorders	22 (12.7)	-	35 (19.4)	1 (0.6)	57 (16.1)	1 (0.3)
Vision blurred	9 (5.2)	-	21 (11.7)	1 (0.6)	30 (8.5)	1 (0.3)
Mydriasis	13 (7.5)	-	10 (5.6)	-	23 (6.5)	-
Dry eye	1 (0.6)	-	6 (3.3)	-	7 (2.0)	-
GI Disorders	23 (13.3)	5 (2.8)	34 (18.9)	4 (2.3)	57 (16.1)	9 (2.6)
Dry mouth	20 (11.6)	-	31 (17.2)	2 (1.2)	51 (14.4)	2 (0.6)
Constipation	1 (0.6)	2 (1.1)	4 (2.2)	2 (1.2)	5 (1.4)	4 (1.2)
Renal/Urinary	4 (2.3)	1 (0.6)	12 (6.7)	1 (0.6)	16(4.5)	2 (0.6)
Urinary retention	2 (1.2)	-	6 (3.3)	-	8 (2.3)	-
Urinary hesitation	1 (0.6)	-	4 (2.2)	-	5 (1.4)	-
Skin, Sq Tissue	6 (3.5)	2 (1.1)	3 (1.7)	-	9 (2.5)	-
Vascular: HTN	1 (0.6)	3 (1.7)	3 (1.7)	2 (1.2)	5 (1.4)	5 (1.4)
Blood/Lymph	3 (1.7)	-	1 (0.6)	-	4 (1.1)	-
Lab Investigations	4 (2.3)	2 (1.1)	-	1 (0.6)	4 (1.1)	3 (0.9)

Source: Adapted from Table 4.1.1.

Reviewer comment: TEAEs occurring >1% were more numerous in the SB group compared to vehicle. The TEAEs consistent with anticholinergic effect and probably related to study drug were ocular, gastrointestinal (dry mouth), and urinary events. No specific pattern could be determined for Skin and subcutaneous Tissue, Lab Investigations, or Blood and Lymphatic systems because the reported terms were individual.

Laboratory Findings

The laboratory evaluations for Trials 301 and 302 were biochemistry, hematology, and urinalysis. Few subjects measured laboratory values outside of the normal range, categorized as normal, high or low normal, and "panic" high or low. The panic abnormal values were assessed, with one exception the SB gel group compared to the vehicle group the numbers of subjects with abnormal values were less than or equal in number.
Abnormal "panic" values were noted for the following assessments:

- Trial 301: alanine aminotransferase (ALT), aspartate aminotransferase (AST), potassium, urine specific gravity.
- Trial 302: ALT, GGT, hemoglobin, urine specific gravity. One SB subject reported elevated sodium level.

Four subjects reported no specific pattern could be determined. In Trial 301, TEAS were reported by four subjects in the SB arm and two in the vehicle arm, while Trial 302 reported one subject in the vehicle arm only with abnormal lab testing.

Any positive pregnancy tests are discussed in Section 8.2.9.

Vital Signs

The vital signs monitored during Study 301 and Study 302 were systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature. Vital signs were reported for subjects at Days 1 (Baseline), 8, 15, 22, 29, 36, 43 (EOT) and 57 (Follow-up visit).

The anticholinergic activity of sofpironium affects the pulse rate (heart rate). The protocol stated that the pulse rate was counted over 60 seconds. The table below captures the Baseline, Day 8 (or first visit after beginning the IP), Day 43 (EOT), and the Follow-up visits. The reported values were comparable between the arms and across the studies. The changes from Baseline for study drug and vehicle were comparable when comparing treatment groups at the same visit, within studies, and between Studies 301 and 302. While the pulse rate change trended lower for the vehicle arms in general, no safety signal was identified.

Table 41: Summary of Pulse Rate Changes for Studies 301 and 302

Pulse Rate (beats/min)	Study 301		Study 302	
	Vehicle	SB 15%	Vehicle	SB 15%
Baseline (n)	176	173	171	180
Mean	74.4	74.4	75.51	75.07
SD	8.71	9.82	10.00	10.89
Median	75.0	74.0	76.00	74.00
Range (max,min)	47, 99	54, 110	49, 102	48, 105
	Value (Change from BL)			
Day 8 (n)	171 (-5)	166 (-7)	164 (-7)	172 (-8)
Mean	73.6 (-0.7)	74.7 (0.1)	74.75 (-0.67)	74.60 (-0.28)
SD	8.55 (8.01)	9.46 (7.74)	10.48 (10.03)	9.89 (9.31)
Median	73.0 (-1.0)	75.0 (0)	74.0 (-1.0)	75.0 (0)
Range (max,min)	47,98 (-22,29)	53, 105 (-20,24)	(47.0, 114.0)	(48.0, 105.0)
Day 43 EOT (n)	162 (-14)	154 (-19)	156 (-15)	159 (-21)
Mean	73.9 (0.6)	75.0 (0.7)	74.79 (-0.4)	74.21 (-0.9)
SD	8.76 (9.17)	9.32 (9.73)	9.25 (9.79)	9.81 (11.09)
Median	74.0 (0)	76.0 (1.0)	74.5 (-0.5)	74.00 (0)
Range (max,min)	52,99 (-27,25)	50,102 (-29,28)	50,104 (-36,28)	50,102 (-45, 29)
Day 57 F-up (n)	162 (-14)	150 (-23)	155 (-16)	159 (-21)
Mean	73.2 (1.1)	74.7 (0.2)	75.20 74.34	75.20 74.34
SD	8.54 (9.55)	10.0 (9.29)	9.888 10.643	9.888 10.643
Median	73.5 (0)	74.0 (0)	74.0 (0)	73.0 (0)
Range (max,min)	51,96 (-23,31)	50,106 (-28,23)	49,109 (-47,31)	53,135 (-31,47)

Max = maximum; Min = minimum; SB = sofpironium bromide; SD = standard deviation
Baseline was defined as Visit 4 or as the last measurement taken on or prior to the first day of dosing if Visit 4 was missing.
Source: Adapted from Study 301 and 302,Table 14.3.6.4

Electrocardiograms (ECGs)

The Applicant conducted clinical study BBI-4000-CL-106, a four-way, crossover, randomized, double-blind, placebo- and active-controlled study to evaluate the effect of a single therapeutic or supratherapeutic dose of sofpironium bromide gel (15%), applied topically, on the QTc intervals in sixty adult healthy subjects. According to the review by Dr. Xutong Zhao, Biometrics, sofpironium bromide did not prolong the QTcF interval in the thorough QT study.

ECGs were evaluated in pediatric subjects 9 years to < 17 years. In Study 105 and Study 108 (which enrolled 105 subjects), the evaluation of electrocardiograms revealed 13 subjects with abnormal ECGs. The changes were considered not clinically significant, and revealed no safety concerns for use in pediatric subjects aged ≥9 to <17 years.

QT

The Applicant evaluated QT/QTc by conducting Study BBI-4000-CL-106 at one US site, from December 2018 completed in March 2019.

BBI-4000-CL-106 was titled: 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.

The primary objective of the study was to evaluate a single supratherapeutic dose of sofpironium 15% gel on the Fridericia-corrected QT interval (QTcF). The secondary objectives were:

1. To evaluate the effect of a single supratherapeutic dose of sofpironium bromide gel, 15% on other electrocardiogram (ECG) parameters (heart rate [HR], PR and QRS intervals, treatment-emergent T-wave morphology, and appearance of U waves);
2. To evaluate pharmacokinetics (PK) of sofpironium and BBI-4010 after administration of a single supratherapeutic dose of sofpironium bromide gel, 15%;
3. To assess the safety and tolerability of a single supratherapeutic dose of sofpironium bromide gel, 15%;
4. To demonstrate assay sensitivity of the study to detect a small QTc effect using 400 mg oral moxifloxacin as a positive control.

Safety was assessed through AE and application site local tolerability assessments, clinical laboratory evaluations (serum chemistry, hematology, urinalysis), physical examinations, vital signs, 12-lead ECGs.

A total of 60 subjects were enrolled and 58 completed the study. No deaths or SAEs were reported, and one subject in the placebo arm was discontinued due to prolonged electrocardiogram QT following placebo (occluded).

Fifty-seven (95%) subjects reported 423 TEAEs: 90% treated with placebo (occluded); 72% of 1038 mg IP (occluded); 29% of 1038 mg IP (occluded); 29% with 173 mg IP plus placebo gel; 21% with moxifloxacin 400 mg. The majority of events (354 [84%]) occurred at the study drug application site.

Application site events (including erythema, pain, exfoliation, and pruritus) occurred in 56 (93%) subjects. While the majority of the events were considered mild or moderate in severity;

severe, nonserious events were reported in three subjects: two subjects reported application site pain with 1038 IP gel (occluded); one subject reported application site exfoliation with 173 mg IP plus placebo gel (unoccluded).

Reviewer comment: This topical drug with anticholinergic activity did not show QT effects during the study. The AEs during the study related to local skin reactions.

Immunogenicity

The immunogenicity of sofpironium 15% gel was not assessed during the phase 3 studies.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant designated the following TEAEs of special interest: vision blurred; mydriasis; urinary retention. The rationale for reporting these events specifically was that these signs and symptoms can be associated with anticholinergic exposure may be the consequence of sofpironium systemic absorption.

- Anticholinergic Exposure Effects

Vision Blurred

The majority of subjects who reported vision blurred were enrolled in the IP arms.

- In Study 301, nine (5.2%) subjects reported vision blurred events of mild (5) or moderate (4) severity. No subjects in the vehicle arm reported vision blurred.
- In Study 302, 21 (11.7%) subjects reported vision blurred with severity of mild (11), moderate (9), or severe (1). In the vehicle arm, one (<1%) subject reported vision blurred of mild severity.

Mydriasis

Mydriasis was reported in the subjects exposed to IP. No subjects in Study 301 and 302 vehicle arms reported mydriasis.

- In Study 301, thirteen (7.5%) subjects reported mydriasis events of mild (7) or moderate (6) severity.
- In Study 302, nine (5.0%) subjects reported mydriasis of mild (2) or moderate (7) severity.

Urinary Hesitation

Urinary hesitation was reported in the subjects exposed to IP. No subjects in Study 301 and 302 vehicle arms reported urinary hesitation.

- In Study 301, one (<1%) urinary hesitation event of mild severity was reported.
- In Study 302, four (2.2%) subjects reported urinary retention of mild (3) or moderate (1) severity were reported.

Reviewer comments: Overall, specific safety issues for subjects exposed to vehicle were isolated. No Study 301 and 302 subjects exposed to vehicle reported mydriasis or urinary hesitation and only one 302 subject reported vision blurred. The submission-specific safety events occurred in those exposed to IP as compared to the vehicle, and are likely or definitely related to sofpironium exposure.

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8.2.5.2. Local Skin Reactions

For this topical drug, local skin reactions (LSR) were monitored, reported and assessed. For total reactions, the rate of LSRs was approximately three-fold higher for the IP group compared to vehicle across each trial and overall. In each pivotal trial, each IP local skin reaction reported at > 1% occurred at a significantly higher rate than in the vehicle group by up to 14-fold. The severity of LSRs was generally mild to moderate, and resolved.

There was one report of contact dermatitis suggestive of an allergic reaction. No hives or urticaria were reported during the pivotal trials.

Table 42: Local Skin Reactions Reported in Phase 3 Trials > 1%

	BBI-4000-CL-301		BBI-4000-CL-302		All	
Application site reaction	SB Gel 15% N = 173 n (%)	Vehicle N = 176 n (%)	SB Gel 15% N = 180 n (%)	Vehicle N = 171 n (%)	SB Gel 15% N = 353 n (%)	Vehicle N = 347 n (%)
Total # Rxns	62 (35.84)	23 (13.07)	81 (45.00)	23 (13.45)	143 (40.51)	46 (13.26)
Pain	11 (6.40)	3 (1.70)	18 (10.0)	3 (1.80)	29 (8.20)	6 (1.70)
Erythema	9 (5.20)	1 (0.60)	14 (7.80)	-	23 (6.50)	1 (0.30)
Dermatitis	11 (6.40)	1 (0.60)	10 (5.60)	-	21 (5.90)	1 (0.30)
Pruritus	12 (6.90)	1 (0.60)	4 (2.20)	1 (0.60)	16 (4.50)	2 (0.60)
Irritation	2 (1.20)	-	6 (3.30)	1 (0.60)	8 (2.30)	1 (0.30)
Exfoliation	3 (1.70)	1 (0.60)	4 (2.20)	-	7 (2.00)	1 (0.30)

Source: FDA Informatics, and Clinical Analysis

Reviewer comments: The LSRs were reported predominantly in the drug treatment arm and likely caused by the study drug. The LSR adverse events can be mitigated and will be listed in labeling.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The COA instruments utilized in this development program, Hyperhidrosis Disease Severity Measure—Axillary, Adult (≥12 years of age) and Child (9-11 years) versions, addressed sweating and wetness only and did not assess subjects safety and tolerability. No analyses were conducted.

8.2.7. Safety Analyses by Demographic Subgroups

Age

Few subjects were enrolled and evaluated age 9 to <12 years in pivotal trials 301 and 302, and few AEs were reported.

- In Study 301, no subject 9 to < 12 years reported an AE.
- In Study 302, one SB-exposed subject age 11 years reported COVID-19 infection. One subject exposed to vehicle reported vision blurred and application site pain and pruritus.

In OL Study 105, one 11–year-old reported application site burning and itching and one 12-year-old reported blurry vision, mydriasis, and application site burning, itching, and stinging.

Reviewer comment: While AEs were reported for subjects 11- and 12-years, there are too few subjects to draw any conclusions regarding safety in the pediatric population 9 to <12 years of age.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant did not conduct an additional study to investigate a specific safety issue or signal.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No safety explorations were conducted by the Applicant. No tumors or cancers were reported during the study.

Human Reproduction and Pregnancy

During Study 301, one pregnancy was reported during the double-blind period. Subject (b) (6) was enrolled in the IP 15% group and discontinued from the study on Day 15 because of a positive pregnancy test. Study drug was discontinued. The subject delivered a

male infant (gestational age 39 weeks) without any congenital abnormalities or clinical problems reported.

During Study 302, no pregnancies were reported.

During the open-label, long-term safety Study 303, two pregnancies were reported.

- Subject (b) (6) received a negative pregnancy test at the Screening Visit. After randomization to IP 5% and a visit five days after screening, a urine pregnancy test was positive; the pregnancy test was confirmed at an unscheduled visit two days later. The subject was discontinued from the study upon pregnancy confirmation and was not exposed to IP. No additional information was collected and the pregnancy outcome unknown.

- Subject (b) (6) was a 25-year-old white female randomized to the IP 15% arm. According to the Applicant, on Day 114 and 116 doses, the subject reported a positive urine pregnancy test was discontinued from the study. Despite multiple attempts to contact the subject for follow-up, no additional information was collected regarding the pregnancy and the outcome was unknown.

Pediatrics and Assessment of Effects on Growth

Phase 3 Study 301 and Study 302 did not assess growth in the pediatric population. Subject height and weight were reported at baseline only.

Two OL studies (BBI-4000-CL-105 [Study 105] and BBI-4000-CL-108 [Study 108]) enrolled subjects in the pediatric population to assess sofpironium gel PK, safety and tolerability. Study 105 recorded height and weight at Baseline only; any change was not assessed, and the measured values were carried over to Study 108.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

For sofpironium gel 15% for the PAH indication, the Applicant assessed overdose by conducting BBI-4000-CL-106 (QT prolongation study) and BBI- 4000-CL-109 (and dose safety study). The one-time dose, 6-fold above the therapeutic dose, did not result in an increase in TEAEs.

Overdose, or the possibility for study drug overdose related to patient use above what is recommended or prescribed. was possible due to human factors as reported during assessment of instruction for use. During the Applicant's human factors study, some subjects reported applying more than one pump. The Applicant did not report more adverse events related to excessive use of study drug during pivotal trials.

The Applicant did not assess the potential for drug abuse potential, or withdrawal or rebound after stopping the drug.

Reviewer comments: The major risk of excessive use (i.e., overdose) of SB gel is the increased opportunity for anticholinergic side effects. According to PK testing, the study drug absorption was low overall and not cumulative, so overdose is less likely.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Sofpironium bromide 5% gel for the treatment of primary axillary hyperhidrosis, marketed as ECCLOCK® in Japan, was approved September 2020. According to the Applicant, they did not identify new safety findings after marketing. The Applicant submitted no reports from the literature.

On January 10, 2023, the Applicant submitted a letter that the studies were concluded, there were no safety reports from the ECCLOCK gel 5%, and they did "not intend to submit a 120-day safety report" to the Agency. Since this application was submitted, one review article regarding hyperhidrosis treatments including SB gel was published (Wong et al., 2022). No new safety signals were identified.

8.2.11. Integrated Assessment of Safety

There are no safety concerns identified in the clinical trial that would impact approvability of the application beyond the concerns regarding the human factors study and instructions for use. Local safety reactions can be adequately described in labeling for prescribers and patients for clinical decision making.

8.3. Statistical Issues

The key statistical issues regarding the interpretability of the findings for Studies 301 and 302 were the impact of multiple enrollments and the challenges with interpreting the gravimetric sweat assessments due to the inherent variability of the assessments and the skewness of the distribution, including outliers. The 4 subjects who were randomized into the two studies under 10 subject IDs had very minimal impact on the efficacy estimates and did not impact the conclusions, whether they were included (ITT) or excluded (mITT) from the analyses.

During the study design stage, the applicant took steps to minimize the impact of the anticipated variability in gravimetric sweat production assessments, particularly by evaluating subjects on three separate days at baseline and end of treatment and using the median assessment to minimize the impact of outliers that might not be replicated on different days.

However, even with the use of median values from within a short time period, the distribution of the GSP values and the change from baseline in GSP was still skewed. The use of ranks rather than the values themselves in the analysis reduces the impact of outliers, however, the use of ranks leads to point estimates and confidence intervals that are not on a clinically meaningful scale, and thus difficult to interpret. Thus, while the p-values from the ranked analysis may be suitable for assessing statistical significance, in order to convey the impact of treatment on a clinically interpretable scale, medians and percentiles of the data on the original scale may be more appropriate. One other issue with the protocol-specified rank analysis, was that the planned rank analysis calculated ranks for the baseline and EOT assessments separately and then calculated the difference in ranks from baseline to EOT for the analysis. An alternative approach would be to calculate the change from baseline in GSP from baseline to EOT, and then calculate the ranks of the observed differences. Note that the 'difference in ranks' approach could be equivalently described as an analysis of the ranks for the EOT values, adjusted for the ranks of the baseline values, whereas the 'ranks of the differences' approach would be more appropriate if the interest was more in the change from baseline differences themselves, rather than just the EOT values. However, regardless of which approach is of interest, the corresponding p-values from both approaches were statistically significant in each study, so the choice of analysis method did not impact the conclusions.

8.4. Conclusions and Recommendations

The clinical trials demonstrated effectiveness. The co-primary efficacy endpoints in clinical trials BBI-4000-CL-301 and BBI-4000-CL-302 in adults were the proportion of subjects with ≥2 point improvement in HDSM-Ax-7 from baseline to EOT and the change from baseline in GSP from baseline to EOT. Both endpoints were statistically significant in each study based on the protocol-specified primary analysis. The Applicant used two clinical outcomes assessment (COA) instruments during the trials, for ages 9 to 11 years and for 12 years and older.

Though variable, the absorption of sofpironium bromide gel was low.

The main safety considerations are anticholinergic side effects, including dilated pupils, blurry vision, dry eye, dry mouth, constipation, and urinary hesitation. The most common local skin reactions >1% and more frequent in the study group vs. vehicle included application site pain, redness, dermatitis and itching. Overall, adverse events were reversible and mild to moderate in severity. ECG changes and cardiac adverse events were not considered clinically significant.

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient or others, or compromised efficacy. Specifically, the review of the human factors study noted that there are risks associated with potential underdose, overdose and inadvertent exposure to others, with symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. The Agency review identified areas of vulnerability that may lead to medication errors.

The review team recommends that Botanix SB, Inc. review the results of the HF validation study along with the root cause analysis and subjective feedback, consider additional design modifications, implement our recommendations, and conduct another HF validation study to demonstrate that the product user interface supports safe and effective use.

Despite the overall conclusion that effectiveness was adequately demonstrated, and that safety events in the clinical trial were not substantial, the deficiencies in the human factors information does not support an approval of this application due to the risks of medication errors and adverse reactions due to inappropriate drug administration. Additional information will be needed to adequately label this product, including patient instructions for use. This issue was communicated to the applicant in a discipline review letter dated September 8, 2023.

The review team recommends a complete response action for this application.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was held as this application did not present any novel or complex regulatory issues, and no other external consultations were requested.

10 Pediatrics

The Applicant requested a partial waiver for pediatric population less than age 9 years under Section 505B(a)(4)(B)(i) of the Pediatric Research Equity Act (PREA). The proposed indication primary axillary hyperhidrosis is correlated with the onset of puberty and has been reported in children as young as 9 years old. The Applicant stated that there was low prevalence of primary axillary hyperhidrosis in the pediatric population younger than 11 years, with values ranging from 0.3% in 6 to11 years to 0.1% in children younger than 6 years old. Based on the low prevalence, completion of studies enrolling children younger than 9 years old would be highly impractical.

The Agency agreed to the Initial Pediatric Study Plan (iPSP) in May 2018. The Applicant submitted amendments dated August 20 and December 18, 2018. In the Amended iPSP, the Applicant eliminated the plan to defer clinical studies in patients 9 to 11 years, and proposed to assess PK and conduct a long-term safety extension study in subjects 9 to < 17 years. In June 2019, the Applicant submitted an Amended iPSP; the Agency reached agreement to the Amended Agreed iPSP in July 2019.

The pivotal studies 301 and 302 enrolled few pediatric subjects but were deemed adequate for the proposed population as the disease process does not differ once pubarche is achieved. Two open-label studies assessed pediatric population 9 to < 17 years. Safety in Study 105 and long-term Study 108 are discussed below.

Study 105

- Study BBI-4000-CL-105 was entitled: Multi-Center, Open-Label Study to Assess Pharmacokinetics, Safety and Tolerability of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to <17 Years of Age, with Axillary Hyperhidrosis

The primary objectives of this study in children were to assess the systemic exposure of sofpironium and its primary metabolite (BBI-4010), and determine the safety profile of IP in pediatric subjects aged ≥ 9 to < 17 years. Subjects with primary axillary hyperhidrosis applied IP once daily topically for 7 days.

Twenty-five subjects were enrolled and completed the study. The subjects' age range was 9 to 16 years with a median of 14 years; 12 subjects (48%) were male and 13 subjects (52%) were female. There were no deaths, or serious or SAEs. Three subjects (12%) reported four TEAEs: dry eye; blurred vision and urinary hesitation; influenza. Two TEAEs were mild and two were moderate in severity. Influenza was considered unrelated, and the eye and urinary disorders events were considered probably or definitely related. Consequently, the dose was not changed. The outcomes were resolved, and all subjects recovered reportedly.

Study 108

- Study BBI-4000-CL-108: A Multi-Center, Open-Label Extension Study to Assess the Long-Term Safety, Tolerability and Pharmacokinetics of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to <17 Years of Age, Previously Enrolled in Studies BBI-4000-CL-105

The primary objectives were to assess the long-term safety and tolerability of IP gel 15%, and determine the systemic exposure of IP and metabolite BBI-4010 in pediatric subjects (aged ≥9 to <17 years) with primary axillary hyperhidrosis following once daily topical application.

As required, all subjects enrolled had completed Study 105. Subjects applied IP gel 15% topically to each axilla once daily for 24 weeks. Twenty-one subjects were enrolled, and 16 subjects (76.2%) completed the study. Two subjects discontinued the study after withdrawal due to AEs, two were withdrawn by the parent/guardian, and one was lost to follow-up.

No deaths or SAEs were reported during the study. Seven subjects (33%) experienced 21 TEAEs, including 4 subjects with 15 events that were considered related to IP treatment. Two subjects (9.5%) discontinued due to a TEAE. The TEAEs were mild or moderate, none was considered severe. TEAEs of specific interest reported were dry eyes (1), dry mouth (1), mydriasis (1), and blurred vision (1).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
Labeling negotiations were not initiated with the applicant due to the deficiencies described above precluding approval in this review cycle. However, risks and benefits of treatment, pending completion of additional human factors information, are such that labeling should be sufficient to adequately inform prescribers and patients. .

12 Risk Evaluation and Mitigation Strategies (REMS)

No additional restrictions or REMS program are recommended at this time.

13 Postmarketing Requirements and Commitment

The application is recommended for a complete response. No postmarketing requirements or commitment are recommended at this time.

14 Division Director (Clinical) Comments

I concur with the review team's Complete Response recommendation, based on the concern for use errors and potential for harm.

Sofpironium gel is a combination drug product composed of the gel within a metered pump container. The cap of the pump container is intended as an applicator; each pump actuation delivers approximately 0.67 mL of the gel formulation. Sofpironium, a new molecular entity and ester analogue of glycopyrrolate, is an acetylcholine receptor antagonist proposed for the treatment of primary axillary hyperhidrosis in adult and pediatric patients 9 years and older. The proposed maximum therapeutic dose is to apply 1 pump of sofpironium bromide gel, 15% (sofpironium topical gel, 12.45%) per underarm once a day at bedtime.

QBREXZA (glycopyrronium) cloth, 2.4%, is a currently marketed anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. Qbrexza is applied once daily to both axillae using a single cloth. Botox (onabotulinumtoxinA) is an acetylcholine release inhibitor and neuromuscular blocking agent approved for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical products; Botox is approved in adult patients and is administered via injection.

Evidence of effectiveness for sofpironium bromide gel, 15% was based on two identical randomized, double-blind, vehicle-controlled multicenter trials (BBI-4000-CL-301 and BBI-4000-CL-302). Subjects applied treatment (sofpironium bromide gel 15% or vehicle) once daily at bedtime to each axilla for 42 days. At baseline, subjects were to have:

- Hyperhidrosis Disease Severity Measure-Axillary-7-item (HDSM-Ax-7) scale score of 3 to 4
- A minimum of 50 mg of sweat production at rest (gravimetric test) in each axilla with a two-axilla combined total of at least 150 mg of sweat production in 5 minutes at room temperature
- Symptoms of axillary hyperhidrosis for ≥6 months' duration

The co-primary efficacy endpoints in these trials were the proportion of subjects with ≥2 point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT) and the change from baseline to EOT in gravimetric sweat production (GSP). Both endpoints were statistically significant in both trials. Results of the secondary endpoints were consistent with the primary endpoint.

Safety findings included an increased incidence of local skin reactions and blurred vision, mydriasis, urinary hesitation and dry mouth in sofpironium-treated subjects compared to vehicle-treated subjects. Urinary hesitation, blurred vision, mydriasis and dry mouth events are consistent with anticholinergic effects resulting from systemic exposure.

The main approvability issue for sofpironium concerns errors in the use of this product. While this topical product has a low systemic absorption, observed adverse events are consistent with anticholinergic systemic exposure. According to the Division of Medication Error Prevention and Analysis I reviewers, "The results of the human factors (HF) validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient or others, or compromised efficacy." Specifically noted were risks associated with potential underdose, overdose and inadvertent exposure to others, with symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Given these risks, I concur with additional risk mitigation recommendations (e.g., design modifications and user interface revisions; modification of the Instructions for Use) and conducting another Human Factors validation study to demonstrate that the revised user interface supports the safe and effective use of the product.

The Applicant developed Child and Adult versions of the HDSM-Ax instrument. The Clinical Outcome Assessment (COA) reviewers concluded that the applicant established content validity and the other measurement properties for the Adult HDSM-Ax-7 scale but not the Child HDSM-Ax-7 scale, partly because of the small sample size (n=5) from the completed qualitative and quantitative research.

Primary axillary hyperhidrosis has a similar clinical presentation in patients ≥9 to <12 years and patients 12 years and older. While the sample size is small, the efficacy data presented by age (Table 22) appear consistent with a treatment effect in subjects ≥9 to <12 years. Based on available safety data, local skin reactions and adverse events consistent with anticholinergic effects were observed in both age groups (≥ 9 to <12 years and ≥ 12 years) and the pharmacokinetic data suggest a lower exposure in the 9-16 year old group compared to adult subjects (see Section 6.2.1 of this review). Taken together, these results suggest that, if approved, sofpironium could be indicated for primary axillary hyperhidrosis patients down to 9 years.

15 Office Director (or designated signatory authority) Comments

The review team and the clinical Division Director recommend a Complete Response for NDA 217347, sofpironium bromide gel for the treatment of primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older, based on the concern for use errors and potential for harm. I concur with this assessment and recommendation.

Sofpironium bromide (proposed proprietary name, Sofdra) 15% gel is a new molecular entity, quaternary ammonium analogue of anticholinergic drug glycopyrrolate, intended to reduce sweat production by selective, competitive inhibition of muscarinic receptor type 3 (M3), which is the predominate receptor in the axillary eccrine glands which provide the watery secretions of hyperhidrosis. Sofpironium bromide gel is to be applied underarm daily at bedtime using a

proprietary device, a metered pump bottle, with an applicator cap over the dispenser and a covering cap; the proposed dosing is one pump actuation per underarm daily at bedtime.

The substantial evidence of effectiveness was established based on two identical randomized, double-blind, vehicle-controlled multicenter trials (BBI-4000-CL-301 and BBI-4000-CL-302). The co-primary efficacy endpoints in these trials were the proportion of subjects with ≥2 point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT) and the change from baseline to EOT in gravimetric sweat production (GSP). Both endpoints were statistically significant in both trials, as detailed in this review. Results of the secondary endpoints were consistent with the primary endpoint. Of note, the Applicant developed Child and Adult versions of the HDSM-Ax instrument. The Clinical Outcome Assessment (COA) reviewers concluded that the Applicant established content validity and the other measurement properties for the Adult HDSM-Ax-7 scale but not the Child HDSM-Ax-7 scale. The Child HDSM-Ax-7 scale was administered to patients younger than 12 years of age which was a small proportion of the patients (n=5). Notwithstanding the shortcomings of the Child HDSM-Ax-7 scale identified by the COA review, the results from that small subgroup were consistent with the efficacy seen in the overall study and given the condition, primary axillary hyperhidrosis, is pathophysiologically similar across the proposed age spectrum, support the conclusion of effectiveness of sofpironium gel in patients 9 to <12 years old.

Safety across the age groups studied was consistent with anticholinergic effects resulting from systemic exposure, including an increased incidence of blurred vision, mydriasis, urinary hesitation, and dry mouth in sofpironium-treated subjects compared to vehicle-treated subjects. Due to enrollment difficulties in the youngest patients, no patients of 9 years of age had been enrolled. However, given the well-characterized safety profile of sofpironium gel across the age spectrum from the clinical program, the well-understood mechanism of action-related risks, and the etiopathogenesis of the disease, there is no reason to expect that the safety risks in 9-year-old patients would be different from that in the older patients.

In summary, the efficacy and safety data summarized above support an overall favorable benefit risk of sofpironium gel for the proposed indication, treatment of primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older.

However, the Division of Medication Error Prevention and Analysis I (DMEPAI) review team has concluded that the user interface does not support the safe and effective use of the proposed product. Specifically, the results of the human factors (HF) validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in risks associated with potential underdose, i.e. compromised efficacy, or overdose and inadvertent exposure to others, with symptoms of local site reaction, transient mydriasis, blurred vision, dry mouth, and urinary hesitation. The DMEPAI team also concluded that the additional mitigations implemented post-validation could not fully mitigate these concerns, and additional risk

mitigations are necessary to address this deficiency, as detailed in the DMEPAI review. I concur with the assessment and recommendation by the DMEPAI team.

Based on the above considerations, the regulatory action for NDA 217347 is a Complete Response.

16 Appendices

16.1. References

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16.2. Financial Disclosure

Covered Clinical Studies BBI-4000-CL-301 and BBI-4000-CL-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 80 (38 investigators [301] and 42 investigators [302])		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

16.3.1. Calculations for multiples of exposures

The following table summarizes the multiples of exposure of sofpironium bromide and its major metabolite BBI-4010 based on AUC comparisons between the NOAEL from nonclinical studies and the maximum recommended human dose (MRHD) from clinical studies. The table provides the multiples described in the product label in the next section. Since pharmacology studies demonstrated that systemic exposure to BBI-4010 is unlikely to induce pharmacologically mediated side effects and multiples of exposures of sofpironium bromide and BBI-4010 are mostly in parallel, multiples of exposures for sofpironium bromide are presented in the labeling section.

Study Type	Dose of Interest (NOAEL in animal studies)	Estimated AUC_{0-t} BBI4000 /BBI4010 (ng·hr/mL)	Multiples of exposure BBI4000 /BBI4010

Human*	15% (107 mg/m^2/day)	119 /82.8	1 / 1
13-week Dermal Mouse, CD1	20%	751/ 995 (male) 350 / 605 (female)	6 / 12 3 / 7
39 Week Dermal Minipig	20%	331/ ND (male) 161 / ND (female)	3 / NA 1 / NA
13 Week Subcutaneous Rat	1.5 mg/kg/day (male) 5 mg/kg/day (female)	345 / 81.3 (male) 1010 / 480 (female)	3 / 1 9 / 6
26 Week Subcutaneous Rat	0.5 mg/kg/day (male) 5 mg/kg/day (female)	116 / 23.3 (male) 1230 /479 (female)	1 / 0.3 10 / 6
Fertility Subcutaneous Rats	10 mg/kg/day	8290 /2860 (male) 2410 / 943 (female)	70 / 35 20 /11
Embryofetal Subcutaneous Female Rats	10 mg/kg/day	3730 / 1800	31 / 22
Embryofetal Subcutaneous Female Rabbits	2 mg/kg/day (embryofetal lethality) 10 mg/kg/day (malformations)	1230 /461 6750 / 2430	10 / 6 57 / 29
Prenatal and postnatal Development Subcutaneous rats	6.0 mg/kg/day (F0 maternal toxicity at 6 mg/kg/day)	Estimated 2238 /1080**	19/13
Juvenile Subcutaneous Rats	5 mg/kg/day	1780 /723 (male) 1330 /390 (female)	15 / 9 11 / 5
Carcinogenicity Subcutaneous Rats	1.5 mg/kg/day (male) 5 mg/kg/day (female)	489 /216 (male) 1380/604 (female)	4 / 3 12 / 7

Carcinogenicity Dermal Mice	20%	228 /500 (male) 1260/450 (female)	2 / 6 11 / 5

*: Animal-to-human exposure multiples were calculated by dividing animal AUC values by human AUC_{0-t} values (combined sex; 24-hour sampling period) observed in Study BBI-4000-CL-103 following administration of sofpironium bromide IPM gel, 15% formulation for 14 days (2 pump actuations of 0.67 mL/actuation (174 mg) equivalent to 107 mg/m^2/day in a 60 kg adult).

** For the prenatal and postnatal study in rats, the sponsor did not conduct any toxicokinetic analysis. The AUC_{0-t} value for this study shown in the table was an estimate and was extrapolated from the rat embryofetal subcutaneous study.

ND: not detectable; NA: not applicable

16.3.2. Nonclinical labeling

Recommended changes to nonclinical information in Highlights of Prescribing Information and sections 8.1, 8.2, 8.3, 8.4, 12.1, and 13.1, 13.2 of the applicant's proposed labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted. The subheadings in Section 8.1 should be in underlined format.

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

16.3.3. Review of Carcinogenicity Studies Conducted with Sofpironium Bromide

Study Title: BBI-4000: Carcinogenicity Study by Subcutaneous Administration to Sprague-Dawley Rats for 104 Weeks

Study no.:	SD18VP
Study report location:	SDN 1, Module 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	sofpironium bromide, lot # T-1, purity 100.9%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Dose selection was based on reduced body weight gain noted in males at 5 mg/kg/day in the 13-week subcutaneous rat study and adverse injection site effects noted in females at 10 mg/kg/day in the 28-day subcutaneous rat study.

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings:
No sofpironium bromide treatment related tumor findings were noted in this study.

Methods

Doses:	Male: 0 (vehicle), 0.3, 0.75, 1.5 mg/kg/day sofpironium bromide Female: 0 (vehicle), 0.5, 1.5, 5.0 mg/kg/day sofpironium bromide
Frequency of dosing:	Once daily
Number/Sex/Group:	72 for main study; 6 for all toxicokinetic groups
Dose volume:	1 mL/kg [The dose volume was split and administered by daily bolus administration to pairs of dose sites (0.5mL/kg/site) on a rotational basis (3 pairs; 6 sites)]
Formulation/Vehicle:	Sterile 0.9 % Sodium Chloride for Injection
Route of administration:	SUBCUTANEOUS
Species:	RAT
Strain:	SPRAGUE-DAWLEY
Age:	5-6 weeks at initiation of treatment.
Comment on Study Design and Conduct:	Hair was removed (via clipping) from the dorsal surface in advance of the first day of dosing and then as deemed necessary during the course of the study.

	Six separate sites on the dorsal body surface were used in pairs. One-half of the dose volume was administered at each of the two sites, each pair site was used in rotation on a daily basis.
Dosing Comments (Dose Adjustments or Early Termination):	None
Dosing Solution Analysis:	Adequate. The concentrations of all doses were within ± 10% of their nominal values.

Observations and Results

Mortality

The numbers of rats surviving to their terminal necropsy were 35 (48.6%), 38 (52.8%), 35 (48.6%), and 35 (48.6%) in the vehicle control, low, medium, and high dose groups, in male rats, respectively, and 20 (27.8%), 31 (43.1%), 18 (25%), and 30 (41.7%) in female rats, respectively. There were no statistically significant differences in mortality across the vehicle control group and the three treated groups in either sex of rats.

Clinical Signs

Over the 104-week dosing period, females in the 5.0 mg/kg/day dose group exhibited a higher incidence of edema, bruising, erythema, and eschar formation at the injection site. In addition, pupil dilation (scored as absent/present) was present at 0.5 to 1 h after dosing in a number of test article treated animals.

There were no test article related effects on the group distribution, multiplicity or mean onset time of palpable masses.

Body Weights

Slightly decreased body weight gains were observed in test article treated groups in comparison with the corresponding controls. The group mean body weight changes in males or females are presented in the following table.

Table 43: Body Weight Gain Data for the Subcutaneous Rat Carcinogenicity Study

Group/sex	1M	2M	4M	5M	1F	3F	5F	6F
Dose (mg/kg/day)	0	0.3	0.75	1.5	0	0.5	1.5	5.0
Period	Body Weight (g) [1]							
Week 0-4	186	186 (100)	180 (97)	189 (101)	93	89 (96)	92 (99)	87 [2] (94)
Week 4-8	98	97 (99)	94 (96)	95 (96)	39	39 (101)	40 (103)	33 [3] (85)
Week 16-32	100	96 (96)	90 [2] (91)	92[b] (92)	35	29 [2] (84)	26 [3] (75)	25 [3] (72)
Week 32-52	73	64 (89)	63 [2] (86)	53 [3] (72)	67	54[c] (80)	52 [3] (78)	43 [3] (65)
Week 52-80	75	73 (98)	59 [2] (79)	60[b] (81)	87	73[2] (84)	65 [3] (75)	60 [3] (69)
Week 0-16	395	384 (97)	375 (95)	389 (99)	170	162 (96)	167 (98)	155 [3] (91)
Week 0-52	567	544 (96)	529 [3] (93)	536 [3] (95)	272	245 [3] (90)	245 [3] (90)	223 [3] (82)
Week 0-104	652	628 (96)	607 (93)	617 (95)	372	357 (96)	321[2] (86)	313 [3] (84)

F=female; M=male

1 Percentages of control are presented in parentheses
2 Statistically significant in comparison with controls $p<0.05$
3 Statistically significant in comparison with controls $p<0.01$

Feed Consumption

The food consumption of females receiving 1.5 or 5.0 mg/kg/day of test article was slightly less when compared to the corresponding control group.

Ophthalmoscopy

No treatment related effects on ophthalmic findings were noted in this study.

Clinical Pathology

Blood samples for hematology and clinical chemistry parameter analysis were collected from 20 animals/sex/group from the main study animals during week 102/103. No treatment related effects were noted on the hematology parameters examined at the end of study.

There were slight changes on the clinical chemistry in the test article treated groups. When compared with the controls, there was an increase in plasma sodium concentration and a decrease in plasma potassium concentration in all test article treated male groups. There was also a slight increase in plasma chloride concentration and an increase in the albumin: globulin ratio in the 1.5 mg/kg/day male group. Protein electrophoresis analysis showed that alpha-2 protein fractions were marginally decreased in all test article treated groups.

Urinalysis

Overnight urine samples for urinalysis parameter analysis were collected from 20 animals/sex/group from the main study animals during week 102/103. No treatment related effects were noted on the urinalysis parameters examined at the end of study.

Gross Pathology

Findings in subcutaneous injection sites (dark area) were noted in all groups during the macroscopic examination.

Histopathology

Peer Review Conducted: Yes
Historical Control Provided for Tumor Incidence: Yes

Histopathology was performed on a standard list of tissues, plus any gross lesions, from all animals including both premature decedents and animals sacrificed at the end of study.

Neoplastic

No statistically significant differences in sofpironium bromide related tumor incidence were observed in rats of either sex in this study, according to the statistical criteria used by the Executive Carcinogenicity Assessment Committee (ECAC).

The Agency statistical reviewer, Dr. Malick Mbodj independently performed the survival and tumor data analyses. The tumor types with p-values less than 0.05 for dose response relationship (trend comparison) and/or pairwise comparisons of vehicle control and treated groups were examined (see table below). Dr. Mobodj listed brain astrocytoma in male rats with a trend comparison p-value less than 0.05. However, no pairwise comparisons were statistically significant for this tumor type. Therefore, this tumor is not considered a treatment related tumor. Dr. Mobodj listed skin and subcutaneous fibrosarcoma in female rats with a trend comparison p-value less than 0.05. However, no pairwise comparisons were statistically significant for this tumor type. Therefore, this tumor is not considered a treatment related tumor.

Table 44: Possible Statistically Significant Tumor Types in Rats

Treated Groups and Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Vehicle Cont (N=72) P - Trend	0.3 mg Low (N=72) P - C vs. L	0.75 mg Med (N=72) P - C vs. M	1.5 mg High (N=72) P - C vs. H
Male	Brain	Astrocytoma	0/72 (59) 0.0341@	1/72 (54) 0.4779	0/72 (56) NC	3/72 (57) 0.1154
Female	Skin And Subcutis	Fibrosarcoma	0/72 (51) 0.0384@	1/72 (52) 0.5049	0/72 (46) NC	3/71 (53) 0.1286

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
@: not Statistically significant at 0.025 for rare tumor in dose response relationship

Non Neoplastic

No test article related effects on non-neoplastic findings were noted in this study.

Injection Site Findings

Histologic findings at the subcutaneous injection sites occurred in all groups, including controls (see table below). These non-neoplastic findings included degenerative/ necrotic changes in the panniculus resulting in its partial/total absence associated with an infiltrate of mononuclear cells and fibrosis. These findings were likely attributed to a minimal local irritant effect of daily repeated subcutaneous sofpironium bromide administration. Hyperplasia of the epidermis,

only noted in 5.0 mg/kg/day female group without evidence of any atypia or pleomorphism indicative of progression to neoplasia, was also considered to be due to a local irritant effect of daily repeated subcutaneous sofpironium bromide injection. These findings are not clinically relevant because of the topical clinical route of administration.

Toxicokinetics
Blood samples were taken on Week 13 and Week 26 for TK evaluation from all dose group toxicokinetic animals. Plasma concentrations of sofpironium and BBI-4010 were measured by a validated LC-MS/MS method. The LLOQs were 0.415 ng/mL for sofpironium and 5.00 ng/mL for BBI-4010.

Toxicokinetic evaluation demonstrated increasing systemic exposure to sofpironium and its major metabolite (BBI-4010) with increasing dose in both sexes without evidence of accumulation.

In vehicle control group, quantifiable plasma sofpironium concentrations were observed in three samples across time points. BBI-4010 was not quantifiable in vehicle control samples. The low levels of sofpironium in three vehicle control group samples do not affect the overall toxicokinetic parameters obtained for this study.
The toxicokinetic parameters are summarized in the following table.

Table 45: Toxicokinetic Parameters for the Subcutaneous Rat Carcinogenicity Study

Group	BBI-4000 Dose level (mg/kg/day)	BBI-4000 C_{max} (ng/mL)				BBI-4000 AUC_{24} (ng·h/mL)			
		Week 13		Week 26		Week 13		Week 26	
		Males	Females	Males	Females	Males	Females	Males	Females
2	0.3	67.9	-	51.4	-	83.9	-	79.7	-
3	0.5	-	103	-	91.8	-	107	-	113
4	0.75	223	-	88.4	-	266	-	239	-
5	1.5	195	235	168	252	399	368	489	511
6	5.0	-	680	-	799	-	1620	-	1380

Text Table 5.2.2.1: Exposure levels for BBI-4010

Group	BBI-4000 Dose level (mg/kg/day)	BBI-4010 C_{max} (ng/mL)				BBI-4010 AUC_{24} (ng·h/mL)			
		Week 13		Week 26		Week 13		Week 26	
		Males	Females	Males	Females	Males	Females	Males	Females
2	0.3	11.1	-	8.28	-	19.3	-	20.0	-
3	0.5	-	10.7	-	14.8	-	23.7	-	32.8
4	0.75	40.0	-	25.3	-	58.9	-	67.8	-
5	1.5	26.0	39.7	52.1	51.4	142	86.1	216	155
6	5.0	-	140	-	124	-	560	-	604

Study Title: BBI-4000 Topical Gel IPM: Carcinogenicity Study by Dermal Administration to CD-1 Mice for 104 Weeks

Study no.:	YV84GG
Study report location:	SDN 1, Module 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Sofpironium bromide gel, 5.0%, Lot # 4005000081601, purity 100.79% Sofpironium bromide gel, 10.0%, Lot # 4005010081601, purity 101.53% Sofpironium bromide gel, 20.0%, Lot # 4005020081601, purity 101.48%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	MFD

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings:
No sofpironium bromide gel treatment related tumor findings were noted in this study.

Methods

Doses:	0 (untreated control, water), 0 (vehicle gel control), 5%, 10%, and 20% sofpironium bromide gel
Frequency of dosing:	Once daily
Number/Sex/Group:	63 for main study; 12 for toxicokinetic animals
Dose volume:	2 ml/kg/day
Formulation/Vehicle:	Hydroxypropyl cellulose, (b) (4) hyxylene glycol, (b) (4) isopropyl myristate, (b) (4) citric acid, (b) (4) dehydrated alcohol (b) (4)
Route of administration:	TOPICAL
Species:	MOUSE
Strain:	CD1(ICR)
Age:	5 weeks at initiation of treatment
Comment on Study Design and Conduct:	Test article was applied daily to a clipped treatment area equivalent to 10% BSA. The treatment site was not occluded. The treatment site was wiped prior to each daily treatment. Some of the control samples were contaminated by the inadvertent reuse of Tyvek over suits for dosing and sample collection.

Dosing Comments (Dose Adjustments or Early Termination):	Due to increased mortality, dosing was stopped when the number of surviving animals by gender reached 20: • Group 5 (20% gel) males stopped dosing on Week 78 when the number of survivors reached 19 • Group 4 (10% gel) males stopped dosing on Week 92 when the number of survivors reached 20 In addition, Group 5 males were terminated at the end of Week 90 when the number of survivors in the group reached 15 (study duration was less than 100 weeks). All other groups continued dosing until the end of the study. The termination criteria for male and female mice in this study received ECAC concurrence.
Dosing Solution Analysis:	Adequate. The concentrations of all doses were within ± 10% of their nominal values.

Observations and Results

Mortality

There was a test article-related increase in mortality in males. Treatment was stopped on Week 78 for the high dose males receiving 20% gel and on Week 92 for the mid-dose males receiving 10% gel. The high dose male group was subsequently terminated on Week 90 when the number of survivors reached 15.

The numbers and percentage of mice surviving to their terminal necropsy were 44 (70%), 39 (62%), 21 (33%), 17 (27%), and 15 (24%), in water control, vehicle control, low, mid, and high dose groups in male mice, respectively, and 26 (41%), 31 (49%), 26 (41%), 32 (51%), and 16 (25%), in female mice, respectively.

The most common factor contributing to death in males was gastrointestinal (GI) tract changes related to sofpironium bromide pharmacologically mediated effects.

Clinical Signs

Sofpironium bromide related clinical observations observed in male groups included reduced body temperature, thin build, hunched posture, partially closed eyelids, abdominal distension, prominent skin turgor, and pallor of the skin.

Tachypnea was observed in females treated with ≥10% sofpironium bromide gel. Dark skin discoloration was reported in males at all dose levels and in females at a dose of 20% gel.

Decreased fecal output (both sexes) and loose feces (males) were reported in all sofpironium bromide gel treated groups.

Erythema was observed at the administration site in the 20% gel groups in both sexes. There were no signs of dermal irritation in either sex in the lower dose groups or controls.

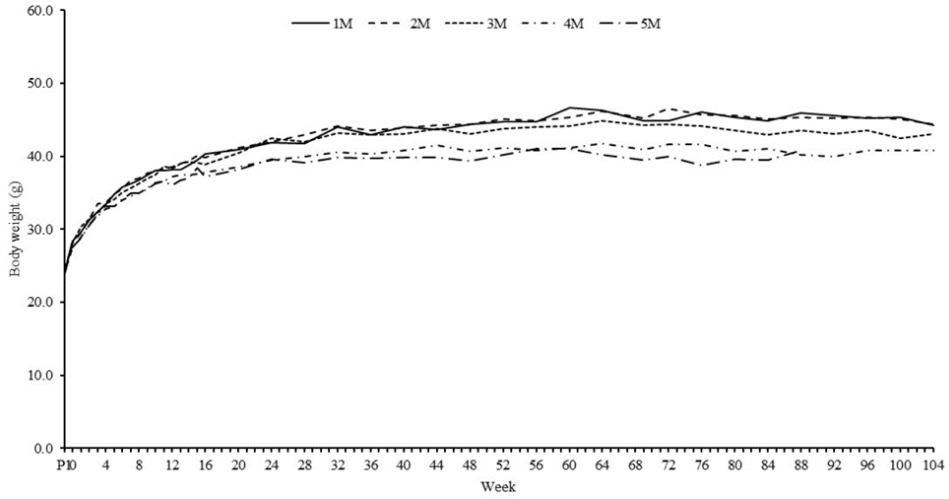
Evaluation of palpable masses showed that the group distribution, multiplicity, and mean onset time were not affected by the dermal administration of sofpironium bromide gel.

Body Weights

There was no test article related effect on the body weight in the low dose male group receiving 5% sofpironium bromide gel.

Body weight was lower, when compared with controls, in males receiving ≥10% sofpironium bromide gel (refer to figure below). Increased body weight gains were observed following the cessation of dosing.

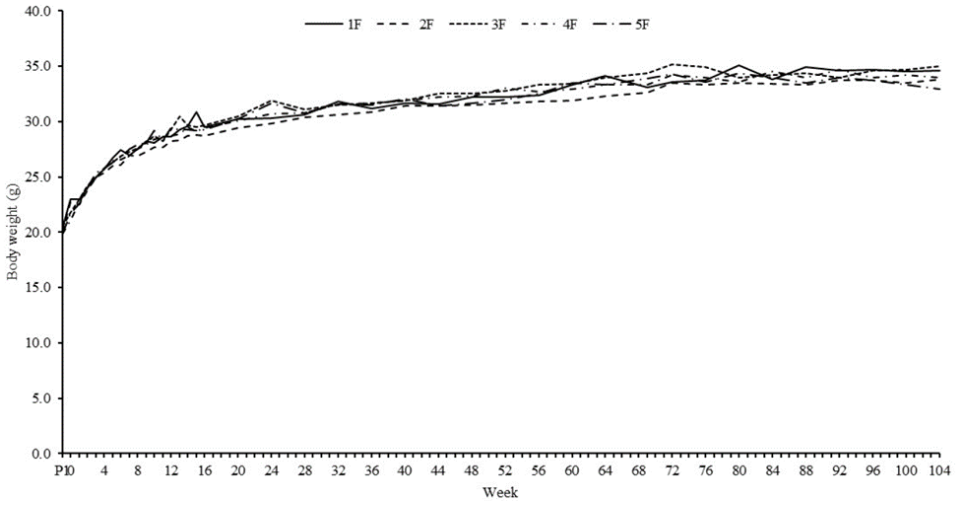
Figure 11: Body Weight Data – Group Mean Values for Male Mice in the Dermal Mouse Carcinogenicity Study



1M: Untreated water control males; 2M: Vehicle control males; 3M: 5% sofpironium bromide gel males; 4M: 10% sofpironium bromide gel males; 5M: 20% sofpironium bromide gel males

The overall body weights for females was not affected by sofpironium bromide gel administration (refer to figure below).

Figure 12: Body Weight Data – Group Mean Values for Female Mice in the Dermal Mouse Carcinogenicity Study



1M: Untreated water control females; 2M: Vehicle control females; 3M: 5% sofpironium bromide gel females; 4M: 10% sofpironium bromide gel females; 5M: 20% sofpironium bromide gel females

Feed Consumption

No treatment related effects on food consumption were noted.

Hematology

Blood samples were collected from all main study animals at scheduled termination (including early termination). No treatment related effects on examined hematology parameters were noted.

Gross Pathology

Macroscopic examination did not reveal any sofpironium bromide related gross observations in either sex in any dose group.

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: Yes

Histopathological examination was performed on a standard list of tissues from all main study treated animals killed at scheduled sacrifice, plus all main-study premature decedents.

Neoplastic

No statistically significant differences in sofpironium bromide gel related tumor incidence were observed in mice of either sex in this study, according to the statistical criteria used by the ECAC.

Dr. Malick Mbodj independently performed the tumor data analyses. The tumor types with p-values less than 0.05 for dose response relationship (trend analysis) and/or pairwise comparisons of vehicle control and treated groups were examined (see table below). Dr. Mbodj listed adrenal adenomas in the mid dose male group with a pairwise comparison p-value less than 0.05. However, the trend analysis was not statistically significant. Therefore, this tumor is not considered a treatment related tumor. There were no statistically significant differences in tumor incidence by pair comparison of untreated (water) control and vehicle control groups.

Table 46: Possible Statistically Significant Tumor Types in Mice

Sex	Organ Name	Tumor Name	0 mg Water Cont (N=63) P - VC vs. W	0 mg Vehicle Cont (N=63) P - Trend	83 mg Low (N=63) P - VC vs. L	149 mg Med (N=63) P - VC vs. M	311 mg High (N=63) P - VC vs. H
Male	Adrenals	Adenoma, Cortical	2/63 (55) NC	0/61 (49) 0.2560	1/61 (40) 0.4494	4/62 (33) 0.0234@	0/63 (21) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
@: not Statistically significant at 0.01 for common tumor in dose pairwise comparison

Non Neoplastic

Non-neoplastic findings were noted in the large intestine and at the topical application site. Dilatation of the rectal lumen was present in both sexes with a slightly higher incidence in the male low dose group (5% gel) (see table below).

Table 47: Non-neoplastic Findings in the Rectum for the Dermal Mouse Carcinogenicity Study

Group/sex	**1M**	**2M**	**3M**	**4M**	**5M**	**1F**	**2F**	**3F**	**4F**	**5F**
Dose (mg/kg/day)	**0**	**0**	**83**	**169**	**355**	**0**	**0**	**83**	**169**	**355**
Number of tissues examined	**44**	**39**	**21**	**17[a]**	**15[b]**	**25**	**31**	**26**	**32**	**16**
Rectum										
Dilatation, Lumen										
Minimal	0	0	0	1	0	0	0	0	0	0
Slight	0	0	5	1	0	0	0	1	0	2
Moderate	0	1	1	0	0	0	0	0	1	0
Total	0	1	6	2	0	0	0	1	1	2

F = female; M = male

[a] dosing ceased at Week 92
[b] dosing ceased Week 78, Group terminated Week 90

Epidermal hyperplasia, characterized by a slight increased thickness of the non-keratinised epidermal layer with no signs of atypia or pleomorphism, was present in females at all dose levels (see table below). This finding was considered to be a minor irritation caused effect.

Table 48: Non-neoplastic Findings in the Skin for the Dermal Mouse Carcinogenicity Study

Group/sex	**1F**	**2F**	**3F**	**4F**	**5F**
Dose (mg/kg/day)	**0**	**0**	**83**	**169**	**355**
Number of tissues examined	**25**	**31**	**26**	**32**	**16**
Topical Application site					
Hyperplasia, Epidermal					
Minimal	1	0	0	0	0
Slight	0	1	13	14	9
Total	1	1	13	14	9

F = female

Toxicokinetics

Blood samples were taken during Week 13 and Week 26 to assess the systemic exposure of male and female mice to sofpironium and BBI-4010. Plasma concentrations of sofpironium and BBI-4010 were measured by a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method. The LLOQs were 0.500 ng/mL for sofpironium and 5.00 ng/mL for BBI-4010.

Toxicokinetic evaluation confirmed systemic exposure to sofpironium and BBI-4010 following dermal administration of sofpironium bromide gel. In water and vehicle control mice, quantifiable plasma sofpironium concentrations were observed at sporadic times however, plasma concentrations of BBI-4010 in the samples taken from the control animals were BLQ in all cases. Based on the sponsor's investigation, it indicated that some of the control samples were likely contaminated by the inadvertent reuse of Tyvek over suits during dosing and sample collection across groups.

In sofpironium bromide gel treated groups, inter-individual variation in plasma sofpironium and BBI-4010 concentrations was high. Systemic exposure to plasma sofpironium and BBI-4010 increased with dose. Sofpironium exposure in females was generally higher than that of males but there was no clear sex difference in BBI-4010 levels at either sampling time point. There was no evidence of accumulation of sofpironium or BBI-4010 between Week 13 and Week 26.

The toxicokinetic parameters are summarized in the following table.

Table 49: Toxicokinetic Parameters for the Dermal Mouse Carcinogenicity Study

Dose (mg/kg/day)		0 Water		0 Vehicle		83		169		355	
Number of Animals (Satellite TK): [1]		M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Sofpironium:											
AUC_{0-23} (ng·hr/mL)	Week 13	NC	NC	NC	NC	104	157	183	267	584	637
	Week 26	NC	NC	NC	NC	45.7	158	191	211	228	1260
C_{max}	Week 13	NC	NC	NC	NC	9.62	17.2	11.1	30.2	40.8	59.8
	Week 26	NC	NC	NC	NC	4.75	65.7	13.7	12.5	18.0	251
BBI-4010:											
AUC_{0-23} (ng·hr/mL)	Week 13	NC	NC	NC	NC	99.3	93.8	293	283	492	352
	Week 26	NC	NC	NC	NC	109	81.1	149	253	500	450
C_{max}	Week 13	NC	NC	NC	NC	9.46	8.93	16.2	26.2	24.3	23.0
	Week 26	NC	NC	NC	NC	10.4	7.72	10.9	24.1	30.7	29.5

[1] Satellite animals used for Toxicokinetic sampling only.

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

16.4.0. Bioanalytical Method Validation

Bioanalytical methods were developed to quantify sofpironium, BBI-4010, and other analytes in human plasma and urine. Three analytical methods were developed to measure sofpironium and BBI-4010 in human plasma, two methods were developed to measure sofpironium and BBI-4010 in human urine, and four methods were used to measure other analytes in human plasma (one method per analyte). The analytical technique used for all analytical methods was high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS).

The list of clinical pharmacology studies is presented in Table 16.4.1.1 below. The table includes clinical studies with PK data. Clinical studies that do not have PK data are not included in this table.

Table 16.4.1.1: Clinical Pharmacology Studies Evaluating PK of Sofpironium Bromide Gel.

Study	Phase	Abbreviated Study Description	Study Design	Dosing Regimen	Study Population/ PK Population
IPM1 Formulation (Intended Commercial Formulation)					
Studies in Adults					
BBI-4000-CL-103	1	A Repeat-Dose Study to Evaluate the Pharmacokinetics of BBI-4000	Single-center, 3-cohort, open-label, randomized, repeat-dose	Sofpironium bromide IPM gel, 5% Sofpironium bromide IPM gel, 15%	n = 10 n = 10 n = 10 All subjects (N = 30) were

		(Sofpironium Bromide) Applied Topically as a Gel in Healthy Subjects		Sofpironium bromide (b) (4) gel, 15% All applied QD x 14 days	healthy adults
BBI-4000-CL-102 (MUPK)	1	A Repeat-Dose Maximum-Use Study to Evaluate the Pharmacokinetics of BBI-4000 (Sofpironium Bromide) Applied Topically as a Gel to Subjects with Hyperhidrosis	Single-center, open-label, nonrandomized, repeat-dose, maximum-use conditions	Cohort A: Sofpironium bromide gel, 15% 1 area (axillae) Cohort B: Sofpironium bromide gel, 15% 3 areas (axillae, palms, thighs) All applied QD x 21 days	n = 12 n = 18 All subjects (N = 30) were adults with axillary hyperhidrosis
BBI-4000-03	1	A Repeat-Dose Study to Evaluate the Pharmacokinetics of BBI-4000 (Sofpironium Bromide) 5%, 10% and 15% Topically Applied Gel in Primary Axillary Hyperhidrosis Patients	Randomized, double-blind, vehicle controlled, repeat-dose	Sofpironium bromide IPM gel, 5% Sofpironium bromide IPM gel, 10% Sofpironium bromide IPM gel, 15% Vehicle gel All applied QD x 28 days	n = 6 n = 6 n = 6 n = 6 All subjects (N = 24) were adults with primary axillary hyperhidrosis
BBI-4000-CL-109	1	An Open-label, Pilot Study to Evaluate the Effect of Occlusion on the Pharmacokinetics, Safety and Tolerability of Topical Sofpironium Bromide Gel in Healthy Adult Subjects	Single-center, open-label, pilot PK, safety and tolerability study	Sofpironium bromide gel, 15%: Therapeutic dose Supratherapeutic dose (6x, occluded) Supratherapeutic dose (6x, unoccluded) All administered once with 7-day washout	N = 12 receive all treatments All subjects were healthy adults.
BBI-4000-CL-106	1	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	Single-center, randomized, double-blind, placebo- and active controlled, crossover.	Sofpironium bromide gel, 15%: Therapeutic dose (1x) Supratherapeutic dose (6x, occluded) Placebo gel (1x, occluded) Moxifloxacin (400 mg, oral) [Randomized, double-blinded (with respect to supratherapeutic dose of sofpironium bromide	N = 60 received all treatments All subjects were healthy adults.

		the QT/QTc Intervals in Adult Healthy Volunteers		gel, 15% / placebo gel only)] All administered once with 7-day washout	
BBI-4000-CL-104	1	An Open-Label, Parallel Group Study to Determine the Effect of Oral Doses of Paroxetine, Cimetidine, and Itraconazole on Sofpironium Bromide (BBI-4000) Pharmacokinetics After a Single Topical Application in Healthy Adult Subjects	Single-center, open-label, 2-part, parallel cohort study	Part 1 (Cohort A) Sofpironium bromide gel, 15% applied QD x 1 day (Day 1) Sofpironium bromide gel, 15% applied QD x 1 day (Day 11) and 20 mg paroxetine HCl QD x 12 days (Days 1-12) Part 2 (Cohort B) Sofpironium bromide gel, 15% applied QD x 1 day (Day 1) Sofpironium bromide gel, 15% applied QD x 1 day (Day 4) and 800 mg cimetidine BID x 5 days (Days 1-5) Sofpironium bromide gel, 15% QD x 1 day (Day 6) and 200 mg itraconazole QD x 7 days (Days 1-7)	Part 1, n = 24 Part 2, n = 24 Subjects were enrolled in Part 1 or Part 2, but not both All subjects (N = 48) were healthy adults
Studies in a Pediatric Population					
BBI-4000-CL-105	1	Multi-Center, Open-Label Study to Assess Pharmacokinetics, Safety and Tolerability of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to <17 Years of Age, with Axillary Hyperhidrosis	Multi-center, open-label PK, safety and tolerability study	Sofpironium bromide gel, 15% Applied QD x 7 days	n = 25 All subjects (N = 24) were pediatric subjects, ≥9 to <17 years of age, with axillary hyperhidrosis.
BBI-4000-CL-108	1	A Multi-Center, Open-Label	Multi-center, open-label	Sofpironium bromide gel, 15%	n = 21 All subjects

		Extension Study to Assess the Long-Term Safety, Tolerability and Pharmacokinetics of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to <17 Years of Age, Previously Enrolled in Study BBI-4000-CL-105	extension long-term safety, tolerability and PK study.	Applied QD x 24 weeks.	(N = 24) were pediatric subjects, ≥9 years to <17 years of age, with axillary hyperhidrosis who participated in and completed Study BBI-4000-CL-105.
(b) (4) Formulation (Historic)					
BBI-4000-CL-201	2	A Multi-center, Randomized, Double Blinded, Vehiclecontrolled Study to Evaluate the Safety and the Effect on Sweat Production of 3 Concentrations of Topically Applied BBI-4000 Gel in Subjects with Axillary Hyperhidrosis	Multi-center, randomized, double-blind, vehicle controlled	Vehicle gel Sofpironium bromide (b) (4) gel, 5% Sofpironium bromide (b) (4) gel, 10% Sofpironium bromide (b) (4) gel, 15% All applied QD x 28 days	n = 46 n = 47 n = 48 n = 48 All subjects (N = 189) were adults with axillary hyperhidrosis
IPM2 (b) (4)					
BBI-4000-05	1	A 14-Day Repeat-Dose Study to Evaluate the Pharmacokinetics of BBI-4000 (Sofpironium Bromide) Gels (IPM1 and IPM2) in Patients with Primary Axillary Hyperhidrosis in Japan	Randomized, double-blind, parallel-group, repeat-dose	Sofpironium bromide IPM1 gel, 15% (with 0.001% citric acid), to each axilla Sofpironium bromide IPM2 gel, 15% (with 0.05% citric acid), to each axilla All applied QD x 14 days.	n = 12 n = 12 All subjects (N = 24) were adults with axillary hyperhidrosis
BBI-4000-08	1	A Pharmacokinetic Study of BBI-4000 Gel in Patients with Primary Axillary Hyperhidrosis in Japan	Single center, open-label, single arm	Sofpironium bromide gel, 5% Applied QD x 12 weeks	N = 25 All subjects had axillary hyperhidrosis

BID = twice daily; CYP = cytochrome P450; (b) (4); DLQI = Dermatology Life Quality Index; GSP = gravimetrically measured sweat production; HDSM-Ax = Hyperhidrosis Disease Severity Measure-Axillary Scale; HDSM-Ax, Child = Hyperhidrosis Disease Severity Measure-Axillary Scale, Child; HDSM-Palm = Hyperhidrosis Disease Severity Measure-Palmar Scale; HDSS = Hyperhidrosis Disease Severity Scale; ICDRG = International Contact Dermatitis Research Group; IPM = isopropyl myristate; PHIS = Palmar Hyperhidrosis Impact Scale; QD = once daily; PGI-C =

Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; QTcF = Fridericia's corrected QT interval; QTcI= QT interval corrected for individuals; US = United States.

Three analytical methods which were developed to measure sofpironium and BBI-4010 in human plasma are summarized as below:

SOP CA 13649-01 - LC-MS/MS Method for the Determination of Sofpironium and BBI-4010 in Acidified Human Plasma (NaF/EDTA)

This method was for the quantitative analysis of sofpironium and BBI-4010 in acidified human plasma (NaF/ethylene diamine tetra acetic acid [EDTA]) using high performance liquid chromatography (HPLC) with mass spectrometric detection. Analytes and internal standards were extracted from acidified human plasma using a protein precipitation procedure. The extracted samples were analyzed by HPLC/MS/MS triple quadrupole mass spectrometer using an electrospray ionization (ESI) source. The calibration range of this assay is 0.0500 to 10.0 ng/mL for sofpironium and 0.100 to 20.0 ng/mL for BBI-4010. Quantitation was determined using a weighted linear regression analysis ($1/concentration^2$) of peak area ratios of the analytes and stable labeled internal standards (deuterated sofpironium bromide [D9-SGE] for sofpironium, and deuterated BBI-4010 [D9-SGA]).

AL-6386-G – Assay Method for the Determination of Sofpironium and BBI-4010 in Human Plasma by LC/MS/MS

This method was for the quantitative analysis of sofpironium and BBI-4010 in acidified human plasma (NaF/EDTA) using HPLC with mass spectrometric detection. Analytes and internal standards were extracted from acidified human plasma using a protein precipitation procedure. The extracted samples were analyzed by HPLC/MS/MS triple quadrupole mass spectrometer using an ESI source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. The calibration range of this assay was 0.05 to 10 ng/mL for sofpironium and 0.1 to 20 ng/mL for BBI-4010. Quantitation was determined using a weighted linear regression analysis ($1/concentration^2$) of peak area ratios of the analytes and internal standards (D9-SGE for sofpironium, and D9-SGA for BBI-4010).

TM17-389 - Determination of Sofpironium and BBI-4010 from Human Disodium EDTA/Sodium Fluoride Plasma (Acidified with 20% Formic Acid 9:1, v/v)

This method was for the quantitative analysis of sofpironium and BBI-4010 extracted from acidified human plasma (NaF/EDTA) by acetonitrile precipitation and analyzed by HPLC/MS/MS. The dynamic range of this assay was 0.0500 to 25.0 ng/mL for both analytes. Acetonitrile precipitation and HPLC/MS/MS were used to determine the concentration of the analyte present in the matrix. An aliquot of the extract was injected onto an HPLC/MS/MS triple quadrupole mass spectrometer. The peak area of the product ion of each analyte was measured against the peak area of the product ion of the stable label internal standards (D9-SGE for sofpironium, and D9-SGA for BBI-4010). A calibration curve for each analyte spanning the curve range and containing at least six concentrations in duplicate was used to quantify the analyte concentration.

The summary from validation reports of the analytical methods used in the clinical pharmacokinetic studies for the determination of sofpironium and BBI-4010 in human plasma is described in following Table 16.4.1.2.

Table 16.4.1.2 Sofpironium and BBI-4010 in Plasma Bioanalytical Assay Details

CRO/Assay	(b) (4)					
Method	SOP CA 13649		AL-6386-G		TM17-389	
Analyte (s)	Sofpironium	BBI-4010	Sofpironium	BBI-4010	Sofpironium	BBI-4010
Lower limit of quantification	0.05 ng/mL	0.100 ng/mL	0.05 ng/mL	0.100 ng/mL	0.05 ng/mL	0.100 ng/mL
Upper limit of quantification	10.0 ng/mL	20.0 ng/mL	10.0 ng/mL	20.0 ng/mL	25.0 ng/mL	25.0 ng/mL
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 9	Number of standard calibrators from LLOQ to ULOQ: 9	Number of standard calibrators from LLOQ to ULOQ: 9	Number of standard calibrators from LLOQ to ULOQ: 9	Number of standard calibrators from LLOQ to ULOQ: 8	Number of standard calibrators from LLOQ to ULOQ: 8
	Cumulative accuracy (%bias) from LLOQ to ULOQ: -2.7 to 3.3%	Cumulative accuracy (%bias) from LLOQ to ULOQ: -2.0 to 2.7%	Cumulative accuracy (%bias) from LLOQ to ULOQ: 85.7 to 113.4%	Cumulative accuracy (%bias) from LLOQ to ULOQ: 86.9 to 114.0%	Cumulative accuracy (%bias) from LLOQ to ULOQ: -1.2 to 1.4%	Cumulative accuracy (%bias) from LLOQ to ULOQ: -1.2 to 1.0%
	Cumulative precision (%CV) from LLOQ to ULOQ: ≤4.0%	Cumulative precision (%CV) from LLOQ to ULOQ: ≤2.7%	Cumulative precision (%CV) from LLOQ to ULOQ: Not calculated	Cumulative precision (%CV) from LLOQ to ULOQ: Not calculated	Cumulative precision (%CV) from LLOQ to ULOQ: ≤5.9%	Cumulative precision (%CV) from LLOQ to ULOQ: ≤8.0%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs: -8.8 to 0.5%	Cumulative accuracy (%bias) in 4 QCs: -10.6 to -3.3%	Cumulative accuracy (%bias) in 4 QCs: 104.6 to 106.0%	Cumulative accuracy (%bias) in 4 QCs: 100.7 to 104.0%	Cumulative accuracy (%bias) in 4 QCs: 0.4 to 5.6%	Cumulative accuracy (%bias) in 4 QCs: -8.6 to 4.6%
	Inter-batch %CV: ≤10.8%	Inter-batch %CV: ≤8.4%	Inter-batch %CV: ≤7.4%	Inter-batch %CV: ≤8.8%	Inter-batch %CV: ≤6.6%	Inter-batch %CV: ≤17.4%
Short Term Stability: Benchtop stability	Cumulative Short-Term Stability: 51 hours in polypropylene tubes in an ice water bath under white light (total of all thaw cycles). Post-Preparative Stability: 121 hours in a polypropylene 96 well plate at 5°C.	Cumulative Short-Term Stability: 51 hours in polypropylene tubes in an ice water bath under white light (total of all thaw cycles). Post-Preparative Stability: 121 hours in a polypropylene 96 well plate at 5°C.	Cumulative Short-Term Stability: 51 hours in polypropylene tubes in an ice water bath under white light (total of all thaw cycles). Post-Preparative Stability: 121 hours in a polypropylene 96 well plate at 5°C.	Cumulative Short-Term Stability: 51 hours in polypropylene tubes in an ice water bath under white light (total of all thaw cycles). Post-Preparative Stability: 121 hours in a polypropylene 96 well plate at 5°C.	4.1 hours (6.7 hours for samples >ULOQ) at ambient temperature	4.1 hours (6.7 hours for samples >ULOQ) at ambient temperature.
Short Term Stability: Freeze -thaw cycles	6 freeze (-80°C)-thaw (ice water bath) cycles in polypropylene tubes under white light.	6 freeze (-80°C)-thaw (ice water bath) cycles in polypropylene tubes under white light.	6 freeze (-80°C)-thaw (ice water bath) cycles in polypropylene tubes under white light.	6 freeze (-80°C)-thaw (ice water bath) cycles in polypropylene tubes under white light.	Demonstrated for 4 cycles at -70°C.	Demonstrated for 4 cycles at -70°C.
Long Term Stability	477 days in polypropylene tubes at -80°C.	335 days in polypropylene tubes at -80°C	477 days in polypropylene tubes at -80°C	335 days in polypropylene tubes at -80°C	124 days at -70°C.	124 days at -70°C.

CV = coefficient of variants; d9-SGA = deuterated BBI-4000; EDTA = ethylene diamine tetraacetic acid; LC-MS/MS = high performance liquid chromatography with tandem mass spectrometry; IS = internal standard; LLOQ = lower limit of quantitation; QC = quality control; ULOQ = upper limit of quantitation; v/v = volume per volume.

(Source: Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods (section 2.7.1), Table 9 to 17., Pages 28 to 66)

Bioanalytical Methods in Urine:

Similar to the bioanalytical methods in human plasma, sensitive and specific LC-MS-MS assays for the determination of sofpironium and BBI-4010 in human urine were developed, validated by two bioanalytical service providers.

SA160101 Analytical Method of BBI-4000 and BBI-4010 Concentrations in Human Urine

This method was for the quantitative analysis of sofpironium and BBI-4010 extracted from human urine (acidified with 100 mg/mL citric acid 9:1, v/v) by acetonitrile precipitation and analyzed using HPLC with mass spectrometric detection. Samples were analyzed by HPLC/MS/MS triple quadrupole mass spectrometer using an ESI (electrospray ionization) source. Positive ions were monitored in the MRM mode. The calibration range of this assay was 0.05 to 10 ng/mL sofpironium and 0.1 to 20 ng/mL for BBI-4010. Quantitation was determined using a weighted linear regression analysis (1/concentration^2) of peak area ratios of the analytes and internal standards. This method was used in Study BBI-4000-03.

TM17-390 Determination of Sofpironium and BBI-4010 from Human Urine (Acidified with 20% Formic Acid 9:1, v/v)

This method is for the quantitative analysis of sofpironium and BBI-4010 extracted from human urine (acidified with 20% formic acid 9:1, v/v) by acetonitrile precipitation and analyzed by HPLC/MS/MS. The dynamic range of this assay is 0.0500 to 25.0 ng/mL for sofpironium, and 0.100 to 50.0 ng/mL for BBI-4010; concentrations higher than the upper limit of quantitation (ULOQ) may be accommodated by dilution with blank matrix. An aliquot of the extract is injected onto an HPLC/MS/MS triple quadrupole mass spectrometer. The peak area of the product ion of each analyte is measured against the peak area of the product ion of the stable label internal standards (D9-SGE for sofpironium, and D9-SGA for BBI-4010). A calibration curve for each analyte spanning the curve range and containing at least six concentrations in duplicate is used to quantify the analyte concentrations.

The summary from validation reports of the analytical methods used in the clinical pharmacokinetic studies for the determination of sofpironium and BBI-4010 in human urine is described in following Table 16.4.1.3.

Table 16.4.1.3 Sofpironium and BBI-4010 in Urine Bioanalytical Assay Details

CRO/Assay	(b) (4)			
Method	TM17-390		SA160101	
Analyte (s)	Sofpironium	BBI-4010	Sofpironium	BBI-4010
Lower limit of quantification	0.05 ng/mL	0.100 ng/mL	0.05 ng/mL	0.100 ng/mL
Upper limit of quantification	25.0 ng/mL	50.0 ng/mL	10.0 ng/mL	20.0 ng/mL

Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Number of standard calibrators from LLOQ to ULOQ	8	Number of standard calibrators from LLOQ to ULOQ	8	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-4.0 to 2.7%	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.8 to 3.3%	Cumulative accuracy (%bias) from LLOQ to ULOQ	93.9 to 110.0%	Cumulative accuracy (%bias) from LLOQ to ULOQ	93.5 to 108.5%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.9%	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.6%	Cumulative precision (%CV) from LLOQ to ULOQ	Not calculated	Cumulative precision (%CV) from LLOQ to ULOQ	Not calculated
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	-11.4 to -4.8%	Cumulative accuracy (%bias) in 4 QCs	-10.0 to 4.0%	Cumulative accuracy (%bias) in 4 QCs	102.1 to 106.0%	Cumulative accuracy (%bias) in 4 QCs	100.0 to 106.0%
	Inter-batch %CV	≤7.5%	Inter-batch %CV	≤9.6%	Inter-batch %CV	≤9.6%	Inter-batch %CV	≤8.5%
Short Term Stability: Benchtop stability	6.3 hours on the benchtop at ambient conditions.		6.3 hours on the benchtop at ambient conditions.		Short term stability: 48 hours at 4°C. Processed samples: 47 hours in autosampler at 5°C. In urine: 7 hours at 4°C, 7 hours on ice.		Short term stability: 48 hours at 4°C. Processed samples: 47 hours in autosampler at 5°C. In urine: 7 hours at 4°C, 7 hours on ice.	
Short Term Stability: Freeze - thaw cycles	6 freeze-thaw cycles at -70°C.		6 freeze-thaw cycles at -70°C.		5 cycles at -80°C and thawing on ice. 5 cycles at -20°C and thawing on ice.		5 cycles at -80°C and thawing on ice. 5 cycles at -20°C and thawing on ice.	
Long Term Stability	82 days (112 days for samples >ULOQ) at -70°C.		112 days at -70°C.		63 days at -80°C. 63 days at -20°C.		63 days at -80°C. 63 days at -20°C.	

CV = coefficient of variation; D9-SGA = deuterated BBI-4010; D9-SGE = deuterated sofpironium bromide; HPLC-MS/MS = high performance liquid chromatography with tandem mass spectrometry; HQC = high level QC; IS = internal standard; LLOQ = lower limit of quantitation; LQC = low level QC; MF = matrix factor; MQC = middle level QC; QC = quality control; ULOQ = upper limit of quantitation.

(Source: Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods (section 2.7.1) Table 918 to 21., Pages 67 to 80)

16.4.1. Population Pharmacokinetics

Following application of sofpironium bromide gel topically, there is some evidence of systemic absorption. A population pharmacokinetic (PopPK) analysis was conducted seeking to leverage pooled data from adult subjects, both with or without axillary hyperhidrosis, as well as children and adolescents with axillary hyperhidrosis. The objective was to establish a structural model for sofpironium bromide and to investigate covariates that might influence systemic exposure.

Various PopPK models were tested using the pooled data. In an effort to enhance model accuracy and stability, several methods were explored. These included the exclusion of data related to non-isopropyl myristate (IPM) formulation, modeling exclusively the IPM formulation of sofpironium bromide gel, 15% and testing covariate effects on bioavailability, such as dose level, dose frequency, formulation, and topical occlusion, etc. Among the models investigated, the 2-compartment structural model with application effect on central volume of distribution (Vc) demonstrated the most appropriate fit. However, it is important to acknowledge that there was

substantial variability and erratic concentration-versus-time profiles observed in the individual-level diagnostics. Such variability is not unexpected for a topically administered product with limited systemic absorption. Even when dosage was included as a covariate on the Vc, the estimated inter-individual variability for central clearance, central volume, and the absorption rate remained notably high at 160.8%, 160.3%, and 230.2%, respectively.

A decision was subsequently made to employ a model-independent, noncompartmental analysis (NCA) rather than relying on a model-simulated exposure for the safety assessment that followed. During NCA parameter estimation, plasma concentrations below the lower assay limit of quantitation were imputed as half of the lower limit of quantitation. Exposure parameters (maximum plasma concentration [Cmax] and area under the plasma concentration-versus-time curve from time 0 to 24 hours postdose [AUC0-24]) were determined for each available dense sampling study day. The highest exposure metric for an individual subject was selected for inclusion in the safety exposure-response (E-R) analysis.

16.4.2. Safety Exposure-Response Analyses

The objective of the safety exposure-response (E-R) analysis was to assess treatment-emergent adverse events (TEAEs) consistent with the known adverse effect profile for drugs with anticholinergic activity.

The Cmax and AUC0-24 estimated utilizing NCA approach for each analysis day were summarized in Table 1. The TEAEs included blurred vision, mydriasis, urinary hesitation, and dry mouth. The number of available observations and occurrences (%) of TEAEs for each safety endpoint by Cmax and AUC0-24 quartile are summarized in Table 2 and Table 3, respectively.

Logistic regression approaches were employed to quantify the relationship between sofpironium exposure and safety endpoints associated with anticholinergic activity, specifically treatment-emergent blurred vision, mydriasis, urinary hesitation, and dry mouth. As a result, logistic regression revealed a statistically significant relationship between AUC0-24 and treatment-emergent blurred vision (Table 4 and Figure 1). A non-significant trend was observed for treatment-emergent dry mouth. No trend was observed for treatment-emergent urinary hesitation (incidence <5%) and no treatment-emergent mydriasis cases were observed in the safety E-R population. Age, race, sex, body size, and disease status were considered as covariates of interest for safety E-R modeling. Due to the correlation between disease status and other covariates, disease status was excluded from covariate analysis. None of these predictors were reliably estimated to be included in the final E-R model for treatment-emergent blurred vision. The predictive performance of E-R model was demonstrated from the visual predictive checks (VPCs) (Figure 2).

Table 1. Summary of Cmax and AUC0-24

Study	Treatment	C_{max}, Mean (SD)					AUC_{0-24}, Mean (SD)				
		Day 1	Day 14	Day 16	Day 21	Day 29	Day 1	Day 14	Day 16	Day 21	Day 29
BBI-4000-CL-103	5% Gel	6.72 (20.7)	1.98 (2.95)	NA	NA	NA	6.02 (11)	28.1 (40.9)	NA	NA	NA
	15% Gel	3.83 (14.1)	7.04 (13.3)	NA	NA	NA	17.2 (42.1)	79.8 (128)	NA	NA	NA
BBI-4000-CL-102	15% IPM (normal use)	2.04 (6.04)	NA	NA	1.6 (2.93)	NA	19.7 (57.1)	NA	NA	12.9 (21.5)	NA
	15% IPM (maximum use)	1.45 (2.07)	NA	NA	0.749 (1.03)	NA	16.5 (25.8)	NA	NA	8.4 (13.9)	NA
BBI-4000-CL-109	15% IPM (normal use)	0.397 (0.568)	NA	NA	NA	NA	2.69 (3.48)	NA	NA	NA	NA
	15% IPM (maximum use)	14.4 (47.1)	NA	NA	NA	NA	53.6 (165)	NA	NA	NA	NA
	15% IPM (maximum use) (occlusion)	5.09 (7.54)	NA	NA	NA	NA	55.7 (71.1)	NA	NA	NA	NA
BBI-4000-CL-105	15% IPM	1.32 (3.16)	NA	NA	NA	NA	15.3 (34.7)	NA	NA	NA	NA
BBI-4000-03	5% IPM	0.511 (0.833)	NA	2.09 (2.83)	NA	0.45 (0.407)	2.61 (4.29)	NA	19.8 (32.3)	NA	5.65 (6.41)
	10% IPM	1.4 (2.41)	NA	2.05 (3.79)	NA	3.53 (7.6)	4.14 (5.62)	NA	16.9 (29.6)	NA	21.2 (43.3)
	15% IPM	4 (6.08)	NA	6.8 (5.71)	NA	11 (10.3)	23.5 (33.7)	NA	51.6 (56.9)	NA	61 (60.5)

Source: BRIC-PMX-SOFP-3091-ER_v6.html
Notes: Gel treatment connotes either IPM or (b) (4) gel formulation.
Abbreviations: AUC_{0-24}= area under the plasma concentration-versus-time curve from time 0 to 24 hours postdose; C_{max}=maximum plasma concentration; NA=not available; SD=standard deviation

Source: Table 16, Population PK and Exposure-Response Modeling and Simulation of Sofpironium Bromide Gel

Table 2. Summary of Safety Endpoint Occurrence (%) by Cmax Quartile

TEAE, n (%)	Sofpironium C_{max} Quartile			
	[0,0.194) (N=57)	[0.194,0.916) (N=57)	[0.916,4.05) (N=57)	[4.05,164] (N=58)
Blurred vision	0 (0)	0 (0)	2 (4)	10 (17)
Dry mouth	1 (2)	1 (2)	5 (9)	6 (10)
Mydriasis	0 (0)	0 (0)	0 (0)	0 (0)
Urinary hesitation	0 (0)	0 (0)	1 (2)	1 (2)

Source: BRIC-PMX-SOFP-3091-ER_v6.html
Abbreviations: C_{max}=maximum plasma concentration; N=number of subjects; n=number of subjects with available data; TEAE=treatment-emergent adverse event

Table 3. Summary of Safety Endpoint Occurrence (%) by AUC0-24 Quartile

TEAE, n (%)	Sofpironium AUC_{0-24} Quartile			
	[0,1.75) (N=57)	[1.75,9.91) (N=57)	[9.91,39.9) (N=57)	[39.9,576] (N=58)
Blurred vision	0 (0)	0 (0)	1 (2)	11 (19)
Dry mouth	1 (2)	1 (2)	3 (5)	8 (14)
Mydriasis	0 (0)	0 (0)	0 (0)	0 (0)
Urinary hesitation	0 (0)	0 (0)	0 (0)	2 (3)

Source: BRIC-PMX-SOFP-3091-ER_v6.html
Abbreviations: AUC_{0-24}=area under the plasma concertation-versus-time curve from time 0 to 24 hours postdose; N=number of subjects; n=number of subjects with available data; TEAE=treatment-emergent adverse event

Source: Tables 17 and 18. Population PK and Exposure-Response Modeling and Simulation of Sofpironium Bromide Gel

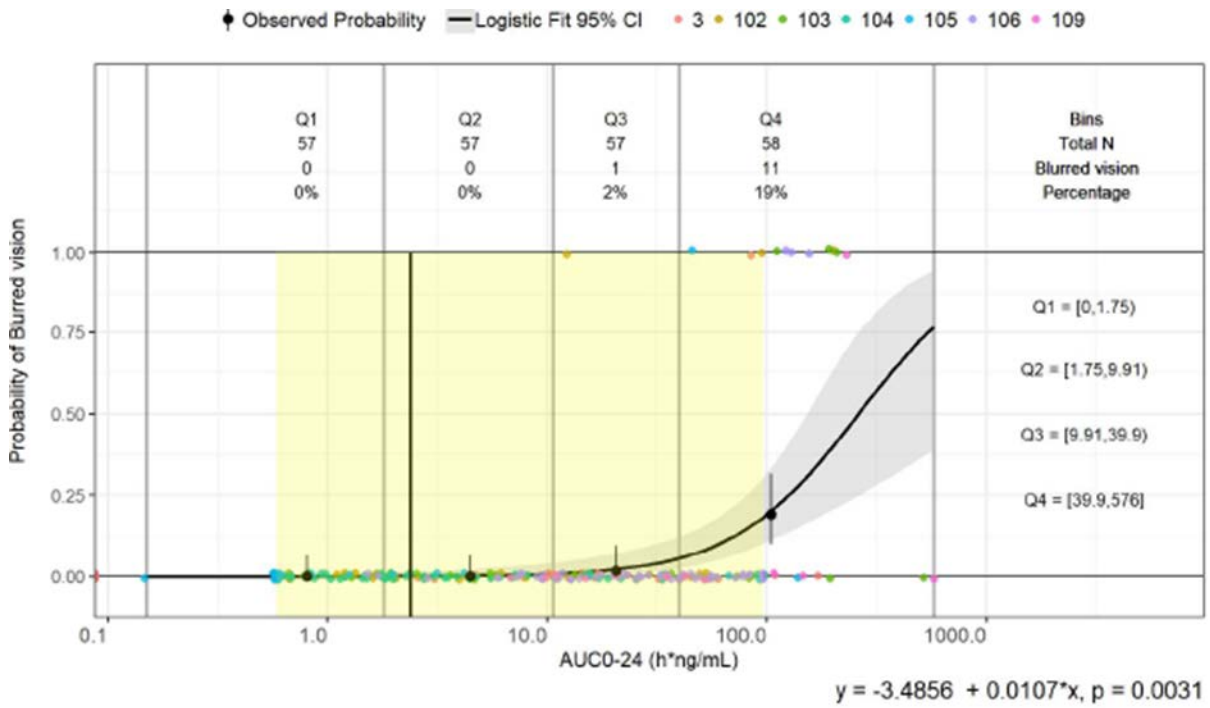
Table 4. Univariate Logistic Regression Analysis Results for Safety Endpoints

TEAE	Exposure	Parameter	Estimate	P-value	AIC
Blurred vision	AUC_{0-24} (hr·ng/mL)	Slope	0.01067	0.0031	84.65
Blurred vision	C_{max} (ng/mL)	Slope	0.0188	0.1087	96.08
Dry mouth	AUC_{0-24} (hr·ng/mL)	Slope	0.00439	0.0931	101.6
Dry mouth	C_{max} (ng/mL)	Slope	0.009359	0.5049	103.5
Urinary hesitation	AUC_{0-24} (hr·ng/mL)	Slope	0.004152	0.4332	26.55
Urinary hesitation	C_{max} (ng/mL)	Slope	0.01632	0.4237	26.57

Source: BRIC-PMX-SOFP-3091-ER_v6.html
Abbreviations: AIC= Akaike information criterion; AUC_{0-24}=area under the plasma concertation-versus-time curve from time 0 to 24 hours postdose; C_{max}=maximum plasma concentration; TEAE=treatment-emergent adverse event

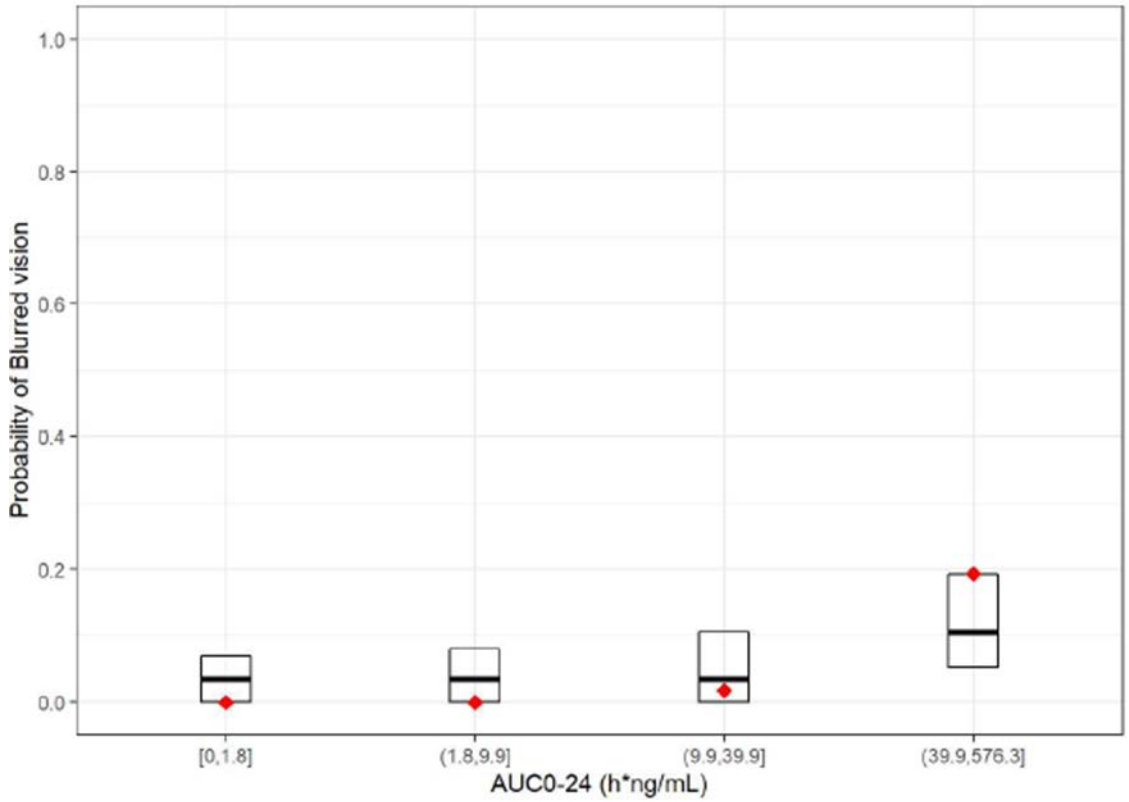
Source: Tables 19. Population PK and Exposure-Response Modeling and Simulation of Sofpironium Bromide Gel

Figure 1. Relationship Between Exposures and Probability of Treatment-Emergent Blurred Vision Occurrence



Source: Figure 16. Population PK and Exposure-Response Modeling and Simulation of Sofpironium Bromide Gel

Figure 2. VPC Plot - Treatment-Emergent Blurred Vision



Source: Figure 17. Population PK and Exposure-Response Modeling and Simulation of Sofpironium Bromide Gel

The AUC0-24 of the subjects receiving chronic topical administration of the anticipated therapeutic dose of sofpironium bromide gel, 15% (1 pump actuation applied once daily to each axilla) was used to predict the probability of AE occurrence using the final model. There was a positive relationship between sofpironium bromide exposure and TEAE related to blurred vision with higher rate of TEAE observed at highest exposure quartile. While a notably higher incidence of Treatment-Emergent Adverse Events (TEAE) associated with blurred vision was detected in the Q4 exposure quartile compared to the other three quartiles, clinical evidence suggests that the risk of individuals experiencing blurred vision with daily topical application of 15% Sofpironium Bromide Gel is considered to be low. In addition, most subjects treated with sofpironium bromide gel, 15% who experience blurred vision describe it as mild or moderate in severity and transient, meaning it is initially intermittent and then gradually resolves over time. Therefore, the positive relationship between the highest observed systemic exposure (AUC0-24) and blurred vision does not pose a significant safety risk when the gel is used at the intended daily dosage for topical administration.

Reviewer's Comments:

- *Given the substantial variability and erratic PK profiles of the topically applied product, the use of a noncompartmental analysis (NCA) without making any assumptions seems to be a reasonable approach for determining the exposure metric. This metric was utilized as input for the safety exposure-response (E-R) analysis.*

- *The Sponsor has chosen to exclusively perform safety exposure efficacy analyses rather than conducting an exposure efficacy investigation. This decision was based on the fact that the locally administered drug's mode of action primarily affects the targeted local area and is not directly correlated with systemic exposure. This approach is deemed acceptable from a regulatory standpoint.*

- *It's important to note that the AUC0-24 and Cmax used for the safety E-R analyses represent the maximum AUC0-24 and Cmax selected for a subject after multiple drug administrations throughout the entire treatment duration. These values may not have been estimated at the time when side effects were measured during treatment.*

- *While a positive relationship exists between the highest observed systemic exposure (AUC0-24) and blurred vision, there is no significant safety concern associated with the recommended daily topical administration dose of 15% sofpironium bromide gel, as supported by clinical evidence. (Refer to clinical review for further details).*

16.5. COA Instruments

Hyperhidrosis Disease Severity Measure—Axillary **(≥12** years of age) [HDSM-Ax]

INSTRUCTIONS: We are interested in finding out about your current experience with excessive underarm sweating.

- Please consider excessive sweating in your underarms only when selecting the answer to each question.
- For each statement, please provide the response that best describes your experience since you woke up yesterday.
- Please answer ALL questions even if some seem similar to others or seem irrelevant to you.

---

1. Since you woke up yesterday, how often did you experience the following while you were awake?
(Please select the number that best describes your experience.)

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4
b) Underarm sweating for no apparent reason?	0	1	2	3	4

2. Since you woke up yesterday, how severe was your experience with the following? (Please select the number that best describes your experience.)

	I did not experience this	Mild	Moderate	Severe	Very severe
a) Underarm sweating when you felt nervous, stressed or anxious?	0	1	2	3	4
b) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4

c) Underarm sweating after little or no physical exercise?	0	1	2	3	4
d) Underarm wetness?	0	1	2	3	4
e) Underarm sweating for no apparent reason?	0	1	2	3	4
f) Underarm sweating that was unmanageable?	0	1	2	3	4
g) Underarm sweating when you were cool?	0	1	2	3	4

3. Since you woke up yesterday, what was your experience with each of the following? (Please select the number that best describes your experience.)

	Not at all	**Slight**	**Moderate**	**Strong**	**Very strong**
a) Feeling the need to change clothes because of underarm sweating?	0	1	2	3	4
b) Feeling the need to wipe sweat from your underarms?	0	1	2	3	4

SUMMARY QUESTIONS (ANCHORS):

4. Since you woke up yesterday, how much of the time did you experience excessive underarm sweating while you were awake? (Please select the number that best describes your experience.)

0 None of the time
1 A little of the time
2 Some of the time
3 Most of the time
4 All of the time

5. How severe was your underarm sweating AT ITS WORST since you woke up yesterday? (Please select the number that best describes your experience.)

0 I did not have underarm sweating (i.e., completely dry)
1 I had underarm sweating but it was mild (i.e., slightly damp)
2 I had underarm sweating and it was moderate (i.e., damp)
3 I had underarm sweating and it was severe (i.e., wet)
4 I had underarm sweating and it was very severe (i.e., soaking)

6. Patient Global Impression of Severity (PGI-S)

Please choose the response below that best describes the severity of your underarm sweating over the past week.**

0 None
1 Mild
2 Moderate
3 Severe
4 Very severe

7. Patient Global Impression of Change (PGI-C)
Please choose the response below that best describes the overall change in your underarm sweating since you started taking the study medication. †

[ ] Very much better
[ ] Moderately better
[ ] A little better
[ ] No change
[ ] A little worse
[ ] Moderately worse
[ ] Very much worse

* These HDSM-Ax questions can appear slightly different when administered in an electronic format.
**Administered as Question #6 of HDSM-Ax at each assessment
† Administered as Question #7 of HDSM-Ax at the Day 43 (EOT) visit only

Hyperhidrosis Disease Severity Measure—Axillary – Child **(≥9** to < 12 years of age) [HDSM-Ax]

INSTRUCTIONS: We are interested in finding out about your underarm sweating.

- Circle the best answer to each question.
  - Think about sweating in your underarms only.
  - Think about your sweating this morning and yesterday.
- Please answer ALL questions.

_____

1. Since you woke up yesterday, how often did you have these things?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a) Damp or wet clothes from underarm sweating?	0	1	2	3	4
b) Underarm sweating for no reason?	0	1	2	3	4

2. Since you woke up yesterday, how much did you have these things?

	I did not have this	A tiny amount	A little	A lot	A great amount
a) Underarm sweating when you felt nervous, scared, or worried?	0	1	2	3	4
b) Damp or wet clothing from underarm sweating?	0	1	2	3	4
c) Underarm sweating after sitting quietly?	0	1	2	3	4
d) Underarm wetness?	0	1	2	3	4
e) Underarm sweating for no reason?	0	1	2	3	4
f) Underarm sweating that you could not hide?	0	1	2	3	4
g) Underarm sweating when you were not hot?	0	1	2	3	4

3. Since you woke up yesterday, how much did you want to do these things?

	Not at all	A tiny amount	A little	A lot	A great amount
a) Change clothes because of underarm sweating?	0	1	2	3	4
b) Wipe sweat from your underarms?	0	1	2	3	4

4. Since you woke up yesterday, how much of the time did you have underarm sweating?

0 None of the time
1 A little of the time
2 Some of the time
3 Most of the time
4 All of the time

5. Describe your underarm sweating AT ITS WORST since you woke up yesterday?

0 I did not have underarm sweating
1 I had a tiny amount of underarm sweating
2 I had some underarm sweating
3 I had a lot of underarm sweating
4 I had a great amount of underarm sweating

6. Patient Global Impression of Severity (PGI-S)
Please choose the response below that best describes the severity of your underarm sweating over the past week.**

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

7. Patient Global Impression of Change (PGI-C)
Please choose the response below that best describes the overall change in your underarm sweating since you started taking the study medication. †

- ☐ Very much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Very much worse

* These HDSM-Ax questions can appear slightly different when administered in an electronic format.
**Administered as Question #6 of HDSM-Ax at each assessment
† Administered as Question #7 of HDSM-Ax at the Day 43 (EOT) visit only

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRAIG H JOHNSON
09/22/2023 11:45:32 AM

XINGUANG LI
09/22/2023 11:51:40 AM

BARBARA A HILL
09/22/2023 12:06:11 PM

ANDREW C GOODWIN
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DIPAK PISAL
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CHINMAY SHUKLA
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DA ZHANG
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YOUWEI N BI
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SURESH DODDAPANENI
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KATHLEEN S FRITSCH
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SARAH L STOTHERS
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SELENA R DANIELS
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DAVID S REASNER
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ROSELYN E EPPS
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DAVID L KETTL
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SHARI L TARGUM
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NIKOLAY P NIKOLOV
09/22/2023 04:26:34 PM