

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217347Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 10, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217347
Product Name, Dosage Form, and Strength:	Sofdra (sofipironium) topical gel, 12.45%
Applicant Name:	Botanix SB Inc.
FDA Received Date:	June 7, 2024
TTT ID #:	2022-1828-3
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Botanix SB Inc. submitted revised container label and carton labeling received on June 7, 2024 for Sofdra. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Sofdra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Botanix SB Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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^a Patel, M. Label and Labeling Review for Sofdra (NDA 217347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 03. TTT ID: 2022-1828.

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MADHURI R PATEL
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06/11/2024 07:31:56 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: 06/06/24

To: Craig Johnson, Regulatory Project Manager, Division of
Dermatology and Dentistry (DDD)

Roselyn E. Epps, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: Montherson L. Saint Juste, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments Sofpironium topical gel, 12.45%

NDA: 217347

Background:

In response to DDD's consult request dated May 20, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA 217347 submission for sofipironium.

PI/PPI/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 23, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments were sent under separate cover on June 4, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on June 5, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

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MONTHERSON L SAINT JUSTE
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 4, 2024

To: Craig Johnson, PharmD
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Montherson Saint Juste, PharmD, MS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): TRADENAME (sofpironium)

Dosage Form and Route: topical gel, 12.45%

Application Type/Number: NDA 217347

Applicant: Botanix SB, Inc.

1 INTRODUCTION

On December 20, 2023, Botanix SB Inc., submitted for the Agency's review a Class 2 Resubmission of their New Drug Application (NDA) 217347 for TRADENAME (sofpironium) topical gel. This resubmission is in response to the Agency's Complete Response Letter dated September 22, 2023. The proposed indication is for the topical treatment of primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on May 20, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (sofpironium) topical gel .

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TRADENAME (sofpironium) topical gel PPI and IFU received on December 20, 2023, and received by DMPP and OPDP on May 23, 2024.
- Draft TRADENAME (sofpironium) topical gel Prescribing Information (PI) received on December 20, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 23, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level,

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 3, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217347
Product Name, Dosage Form, and Strength:	Sofdra (sofipironium) topical gel, 12.45%
Applicant Name:	Botanix SB Inc.
FDA Received Date:	May 24, 2024
TTT ID #:	2022-1828-2
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Botanix SB Inc. submitted revised container label and carton labeling received on May 24, 2024 for Sofdra. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Sofdra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. The dosage statement includes (b) (4) and the format of the expiration date is not consistent between the container label and carton labeling, which may lead to confusion.

3 RECOMMENDATIONS FOR BOTANIX SB INC.

A. General Comments (Container Label & Carton Labeling)

1. We recommend revising the statement of dosage statement to read either, (b) (4) or "Dosage: see Prescribing Information".

B. Carton Labeling

1. We note the format for the expiration date on the container label has been revised to YYYY-MM-DD. However, the carton labeling is showing as "XXX XXXX" near the 2D data matrix, and as "XXXXXXXXXX" on the bottom flap. Please clarify if all labels and labeling (including the IFU) will use the YYYY-MM-DD expiration date format.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^a Patel, M. Label and Labeling Review for Sofdra (NDA 217347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 17. TTT ID: 2022-1828-1.

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/s/

MADHURI R PATEL
06/03/2024 08:48:17 AM

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06/03/2024 04:21:39 PM

HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 20, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217347
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form and Strength:	Sofdra ^a (sofpironium bromide) topical gel, 15%
Device Constituent:	Multiple dose metered pump
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Botanix SB, Inc. (Botanix)
FDA Received Date:	December 20, 2023, March 7, 2024, March 28, 2024, April 18, 2024
TTT #:	2022-1832-1
DMEPA 1 Team Leader (Acting):	Matthew Barlow, RN, BSN
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

^a The proposed proprietary name, Sofdra, was found conditionally acceptable by DMEPA on March 8, 2024.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 217347 for Sofdra (sofpironium bromide) topical gel.

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information	Section 1.1
Background Information Previous DMEPA HF Reviews	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Labels, Labeling, and Packaging	Appendix C

N/A=not applicable for this review

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Sofdra that Botanix SB, Inc. submitted on December 20, 2023.

Table 2. Relevant Product Information for Sofdra	
Initial Approval Date	N/A
Active Ingredient	sofpironium bromide
Indication	indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older
Route of Administration	topical
Dosage Form	topical gel
Strength	15%
Dose and Frequency	The recommended dose of SOFDRA is 1 pump actuation per underarm administered topically once a day at bedtime, for a daily dose of 174 mg of sofpironium bromide. SOFDRA should not be used more frequently than once every 24 hours.
How Supplied	SOFDRA is supplied in an airless bottle sealed with a multi-dose metered pump, applicator, and cap. Each bottle contains 50 mL of gel with a multi-dose pump capable of dispensing 60 pump actuations.

Storage	Store upright at room temperature of 20°–25°C (68°-77°F); brief excursions permitted to 15°- 30°C (59°-86°F) [See USP Controlled Room Temperature]. SOFDRA is flammable; keep away from heat or flame.
Container Closure/ Device Constituent (including figure)	(b) (4)
Intended Users	Patients (adults and adolescents); Caregivers
Intended Use Environment	Home

1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On May 1, 2024, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, NDA 217347, IND 121256, and sofipironium. The identified reviews and FDA/Applicant interactions are provided below.

- On November 19, 2021, the Applicant submitted a human factors (HF) validation study protocol, and we provided our review and feedback on January 10, 2022^b.
- On September 23, 2022, the Applicant submitted their new drug application (NDA), which included HF validation study results.

^b Oguntimein, O. HF Validation Study Protocol Review for sofipironium bromide (IND 121256). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2021-2263.

- On September 15, 2023, we completed our review and recommended the Applicant revise their proposed product user interface and conduct an HF validation study evaluating the modified user interface^c.
- On September 22, 2023, the application received a complete response (CR) due to HF deficiencies^d.
- On October 27, 2023, the Applicant submitted a Type A meeting request and meeting package. On November 22, 2023, Type A preliminary comments were sent to the Applicant^e, in which we included the following:
 - The Applicant may submit data from their new HF validation study and supporting IFU to support their NDA resubmission; however, the acceptability of the results will be a review issue
 - We continued to recommend modifications to the user interface we had originally communicated in the CR letter.
 - We recommended that the new HF validation study be designed to avoid any use of prompting or leading language that may bias the participants' performance (i.e., directing participants to the IFU, etc.)
 - We recommended the Applicant submit their HF validation study protocol for our review, if any changes were made.
- On December 20, 2023, the Applicant resubmitted their NDA, which included a new HF validation study evaluating their revised user interface. Note, we did not review the HF validation study protocol.
- On February 28, 2024, a Discipline Review letter was sent to the Applicant, in which we informed them of our concerns regarding the methodology of the HF validation study^f. Specifically, we highlighted our concerns regarding the inclusion of knowledge task questions in the middle of the simulated use scenario that may have biased the participants' performance. Additionally, we recommended they conduct a new HF validation study with an acceptable methodology.
- On March 7, 2024, in response to the Discipline Review letter, the Applicant submitted a meeting request and meeting package to address the deficiencies noted in the Discipline Review letter. On March 21, 2024, the meeting request was granted as a Type C written response only (WRO) meeting.
- On March 25, 2024, we sent our final written response to the Applicant^g. In our response, we further clarified our specific concerns with the HF validation study

^c Barlow, M. HF Validation Study Results Review for sofipirionium bromide (NDA 217347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEPT 15. RCM No.: 2021-2263.

^d Johnson, C. Complete Response for sofipirionium bromide. Silver Spring (MD): FDA, CDER, OND, DDD (US); 2023 SEPT 22. NDA 217347.

^e Johnson, C. Type A Meeting Preliminary Comments for Sofdra (sofipirionium bromide). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2023 NOV 22. NDA 217347.

^f Johnson, C. Discipline Review Letter for Sofdra (sofipirionium bromide). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2024 FEB 28. NDA 217347.

^g Johnson, C. Type C Guidance Meeting Final Written Responses for Sofdra (sofipirionium bromide). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2024 MAR 25. NDA 217347.

methodology. Additionally, we requested the Applicant provide any data they have to address our concerns and demonstrate the participants were not biased into referring to the IFU when they otherwise may not have; however, we informed the Applicant, if the data was deemed to be insufficient, the Applicant would have to conduct a new HF validation study.

- On March 28, 2024, the Applicant submitted additional information to address our concerns regarding the HF validation study methodology.
- On April 15, 2024, we sent an advice letter to the Applicant informing them that we maintain our concern and request they conduct a new HF validation study and submit the results for our review^h.
- On April 18, 2024, the Applicant submitted the results from a new HF validation study, which is the subject of this review.

2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study (HFVS) design and our discussion of methodology concerns (as applicable). See Appendix A for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	
User Group(s)	• Pediatric patients [9 to 17 years old] (n=15) • Adult patients [18 years of age and older] (n=15) • Caregivers [18 years of age and older] (n=15)
Training	No participants were trained
Test Environment & Materials	The test room was set up to simulate a home environment where a patient would go to learn about and/or apply the product for the first time. The room was well-lit with a table and chairs for the participant and moderator, a functional sink, and a large mirror, representative of a user's home bedroom/bathroom.
Sequence of Study	1. Simulated use scenario (including doses evaluated) 2. Knowledge tasks questions Root cause analysis (RCA) and subjective data

^h Johnson, C. General Advice Letter for Sofdra (sofipronium bromide). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2024 APR 15. NDA 217347.

3 RESULTS AND ANALYSIS

In this section, we have carefully reviewed each reported use issue (i.e., use error, close call, use difficulty), the Applicant's use-related risk analysis (URRA), the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

The HF validation study showed issues with the tasks evaluated by simulated use and knowledge-based assessments (KBAs) listed below in this section.

- *Remove cap*
 - 2 participants (P24; P26) did not remove the cap from the applicator; however, there was no subjective feedback provided by either participant related to the user interface.
- *Prime the pump*
 - 1 participant (P24) did not prime the pump. This participant stated they were "more focused on the administration steps." Additionally, the Applicant stated it may not have been clear to this participant they had to perform all of the tasks in the study as they asked if they should "do this for real".
- *Applies to both armpits*
 - 1 participant (P3) applied to the same armpit. This was attributed to study artifact as the participant did not realize there was a skin barrier pad on both armpits.
- *Apply 1 pump of gel to applicator for first armpit*
 - 1 participant (P3) began applying the gel with a towel; however, as they were applying, they referenced the IFU and realized this was not correct. They then wiped off the gel that had been applied and re-applied the gel correctly to one armpit (same armpit) using the applicator. The participant attributed this to rushing and not reading the IFU.
 - 1 participant (P24) did not press the pump all the way down when applying the pump of gel to the applicator for both armpits. P24 stated this error was due to rushing. Additionally, the Applicant stated it may not have been clear to this participant they had to perform all of the tasks in the study as they asked if they should "do this for real".
- *Apply gel to first armpit*
 - 1 participant (P12) spilled the gel by tilting the applicator. When they pumped the gel onto the applicator for the first armpit, they inadvertently had the pump pointing at an angle. This caused some of the gel to get pumped near/on the edge of the top of the applicator. While referring to the instructions before applying the gel, they had the applicator tilted in an effort to prevent the gel on the edge from dripping over the side. However, this caused the gel on the top to drip off the back side of the applicator. They self-identified this issue and corrected their behavior for the second armpit.
- *Apply 1 pump of gel to applicator for second armpit*

- See P24 use issue for the task *Apply 1 pump of gel to applicator for first attempt* above.
- *Wash hands*
 - 1 participant (P24) did not wash their hands. This was attributed to the participant rushing and not being clear if they needed to perform all the tasks.
- *Prepare armpits*
 - 1 participant (P24) did not identify to remove all clothing around the armpits before applying the gel. This participant did not provide any subjective feedback. The Applicant stated this participant was observed skimming the IFU.
- *Apply to armpits only*
 - 1 participant (P38) did not identify to not apply Sofdra to broken skin. This participant recommended increasing the size of the red box in Step 6.1 to make it more visible. We note this statement is included in the “Important Information You Need to Know Before Applying” section as well as a caution statement in Step 6.1.

For each observed issue, we considered the participants’ subjective feedback, the Applicant’s URRR, RCA, our evaluation of the overall residual risks, the implementation of best practice standards and the Applicant’s proposed mitigations (including any post-HFVS changes to the user interface). As a result, in this particular instance, we find the proposed user interface has been appropriately designed, and we did not identify recommendations to address the identified issues with these tasks.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated use issues with critical tasks that may result in harm. However, based on our review of the available participants' subjective feedback and root cause analysis, we did not identify additional risk controls to address the use issues at this time. We find the risks have been mitigated to an acceptable level. As such, we have no recommendations for this NDA.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report, use-related risk analysis, and background information can be accessed in EDR via: <\\CDSESUB1\EVSPROD\nda217347\0031\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pah\5354-other-stud-rep\2345\iaa-2345-hf-val-report.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 1/12/2024, we issued an Information Request (IR) to request intend-to-market samples of the proposed product. On 1/18/2024, the Applicant provided an acceptable response.

APPENDIX C. LABELS, LABELING, AND PACKAGING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,ⁱ along with postmarket medication error experiences with similar products, we reviewed the following Sofdra labels and labeling submitted by Botanix SB, Inc. on December 20, 2023

- Container label(s)
- Carton labeling
- Instructions for Use, available from <\\CDSESUB1\EVSPROD\nda217347\0024\m1\us\114-labeling\draft\labeling\sofdra-ifu.pdf>
- Prescribing Information (Image not shown), available from <\\CDSESUB1\EVSPROD\nda217347\0024\m1\us\114-labeling\draft\labeling\draft-label.pdf>

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ⁱ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MATTHEW J BARLOW
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 17, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217347
Product Name, Dosage Form, and Strength:	Sofdra (sofpironium) topical gel, 12.45% ^a
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Botanix SB Inc.
FDA Received Date:	December 20, 2023 and January 22, 2024
TTT ID #:	2022-1828-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

^a We note the Applicant submitted the established name, dosage form, and strength as 'sofpironium bromide, 15%'. However, per Office of Pharmaceutical Quality (OPQ), established name, dosage form, and strength is 'sofpironium topical gel, 12.45%'.

1 INTRODUCTION

As part of the approval process for Sofdra (sofipironium) topical gel, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Sofdra Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Botanix SB Inc. previously submitted NDA 217347 on September 23, 2022, which received a Complete Response letter on September 22, 2023 due to issues with human factors data.^b

Thus, Botanix SB Inc. submitted a Class 2 Resubmission on December 20, 2023.^c

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 217347.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Sofdra Patient Package Insert (PPI) and Instructions for Use (IFU) and determined that they are acceptable from a medication error perspective.

However, the proposed Sofdra Prescribing Information (PI), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Dermatology and Dentistry (DDD) in Section 4 and for Botanix SB Inc. in Section 5. Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. Section 2 Dosage and Administration

^b Johnson, C on behalf of Nikolov, N. Complete Response for NDA 217347. Silver Spring (MD): FDA, CDER, OND, Division of Dermatology and Dentistry (DDD) (US); 2023 SEP 22.

^c Resubmission Cover Letter (NDA 217347). King of Prussia (PA): Botanix SB Inc.; 2023 DEC 20. Available from: <\\CDSESUB1\EVSPROD\nda217347\0024\m1\us\12-cover-letters\cover-letter.pdf>.

2. Section 3 Dosage Forms and Strengths

- a. Consider revising (b) (4)

3. Section 16 How Supplied/Storage and Handling

- a. Consider adding the following statement “Each pump actuation (b) (4)
0.67 mL of gel (b) (4)”
- b. Consider revising the “20°–25°C (68°–77°F)” and “15°– 30°C (59°–86°F)” to “20°C to 25°C (68°F to 77°F)” and “15°C to 30°C (59°F to 86°F)”.

5 RECOMMENDATIONS FOR BOTANIX SB INC.

A. General Comments (Container Label(s) & Carton Labeling)

1. The established name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. The strength statement lacks prominence. Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., Total contents statement).
3. The terminology within the statement of dosage statement (b) (4) is inconsistent with the terminology in the Prescribing Information. To ensure

consistency with the terminology in the Prescribing Information. We recommend revising the statement of dosage statement to read, “(b) (4) Dosage: see Prescribing Information.”

4. Revise the statement on the principal display panel (PDP) (b) (4) to read: “Each pump actuation delivers 0.67 mL of gel containing 72 mg of sofpironium”.
5. Remove the statement on the principal display panel (PDP) (b) (4) and revise the Total contents statement from (b) (4) to “Net quantity 50 mL multi-dose metered pump capable of dispensing 60 pump actuations”.
6. Revise the storage temperatures “20°C-25°C (68°F-77°F)” and “15°C- 30°C (59°F- 86°F)” to “20°C to 25°C (68°F to 77°F)” and “15°C to 30°C (59°F to 86°F)”, replacing the dash “-” with “to”.
7. We note the format for the expiration date on the container label is YYYY-MMM, on the carton label it is not clearly defined (XXX XXXX), and on the Instructions for Use (IFU) Step 3 figure shows “MMMYYYY”. Revise all labels and labeling (including the IFU) to reflect the expiration date format consistently. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. *See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*

B. Container Label(s)

1. The linear barcode is oriented in a horizontal position. Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode. We recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode.
2. Relocate “For topical use only” to above the “Use the attached Gel Applicator....” statement for increased prominence.

C. Carton Labeling

1. Consider removing [REDACTED] (b) (4) [REDACTED] from the principal display panel.
2. Relocate “For topical use only” to above the “Apply before bed.” statement for increased prominence.

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Sofdra received on December 20, 2023 from Botanix SB Inc..

Table 2. Relevant Product Information for Sofdra	
Initial Approval Date	N/A
Active Ingredient	sofpironium
Indication	indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.
Dosage Form	topical gel
Strength	12.45%
Route of Administration	topical
Dose and Frequency	The recommended dose is 1 pump actuation per underarm administered topically once a day at bedtime, for a daily dose of 174 mg of sofpironium bromide. Should not be used more frequently than once every 24 hours
How Supplied	supplied in an airless bottle sealed with a multi-dose metered pump, applicator, and cap. Each bottle contains 50 mL of gel with a multi-dose pump capable of dispensing 60 pump actuations NDC 83723-010-50
Storage	Store upright at room temperature of 20°–25°C (68°-77°F); brief excursions permitted to 15°- 30°C (59°-86°F) [See USP Controlled Room Temperature]. Is flammable; keep away from heat or flame.
Container Closure	(b) (4) bottom cover, (b) (4) (Figure 2). The specifications of the 50 mL airless bottle

{

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Sofdra labels and labeling submitted by Botanix SB Inc..

- Prescribing Information received on December 20, 2023, available from <\\CDSESUB1\EVSPROD\nda217347\0024\m1\us\114-labeling\draft\labeling\draft-label-tracked.pdf>
- Patient Package Insert received on December 20, 2023, available from <\\CDSESUB1\EVSPROD\nda217347\0024\m1\us\114-labeling\draft\labeling\patient-info-tracked.pdf>
- Instructions for Use received on January 22, 2024, available from <\\CDSESUB1\EVSPROD\nda217347\0026\m1\us\114-labeling\draft\labeling\sofdra-ifu.pdf>
- Container label(s) received on December 20, 2023
- Carton labeling received on December 20, 2023

B.2 Container Label(s) and Carton Labeling Images

Container label(s)



^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

APPENDIX C. PREVIOUS DMEPA REVIEWS

On May 13, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, '217347'. Our search identified one previous review^e and we considered our previous recommendations to see if they are applicable for this current review.

^e Rahbani, P. Label and Labeling Review for sofpironium (NDA 217347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 02. TTT ID No.: 2022-1828.

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/s/

MADHURI R PATEL
05/17/2024 03:17:38 PM

YEVGENIYA M KOGAN
05/17/2024 05:27:29 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: September 22, 2023

To: Craig Johnson, PharmD
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): TRADENAME (sofipironium bromide)

Dosage Form and Route: topical gel

Application Type/Number: NDA 217347

Applicant: Botanix SB, Inc.

1 INTRODUCTION

On September 23, 2022, Botanix SB, Inc., submitted for the Agency's review an original New Drug Application (NDA) 217347 for TRADENAME (sofpironium bromide) topical gel with a proposed indication for the topical treatment of primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older.

On October 3, 2022, the Division of Dermatology and Dentistry (DDD) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (sofpironium bromide) topical gel.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for TRADENAME (sofpironium bromide) topical gel.

2 CONCLUSIONS

Due to outstanding deficiencies, DDD plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/

SUSAN W REDWOOD
09/22/2023 01:34:22 PM

BARBARA A FULLER
09/22/2023 01:47:53 PM

LASHAWN M GRIFFITHS
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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2022348
NDA#/Referenced IND for NDA:	NDA 217347/Referenced IND 121256 for NDA
Applicant:	Botanix pharmaceuticals
Established Name/Trade Name:	Sofpironium bromide gel
Indication:	Indication: primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older Please check all that apply: ☐ Rare Disease/Orphan Designation ☒ Pediatrics
PDUFA Goal Date:	July 23, 2023
Review Division:	Division of Dermatology and Dentistry (DDD)
Clinical Reviewer:	Roselyn Epps, MD, FAAP, FAAD
Clinical Team Leader (TL)	David Kettl, MD, FAAP
Regulatory Project Manager:	Craig Johnson, PharmD
COA Reviewer:	Sarah Stothers, RN, MSN, MPH
COA TL:	Selena Daniels, PharmD, PhD
COA Division Director:	David Reasner, PhD
Instruments reviewed:	1. Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) Adult and Child versions ☒ Patient-reported outcome (PRO)

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1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of sofpironium bromide gel, 15% for the treatment of primary axillary hyperhidrosis in adult and pediatric patients 9 years of age and older. The specific clinical outcome assessment ((b) (4)) are related to improvement in excessive axillary (underarm) sweating (i.e., decreased severity and frequency of excessive underarm sweating), which are derived from two multicenter, randomized, double-blind, vehicle-controlled studies (Studies BBI-4000-CL-301 and -302).

The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the (b) (4) related to the concept(s) of interest. The co-primary and secondary efficacy endpoints (b) (4) for Studies BBI-4000-CL-301 and -302 are:

- Co-primary efficacy COA endpoint:
 - The proportion of subjects achieving at least a 2-point improvement in the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax-7) scale score¹ from baseline to day 43².
- Secondary efficacy COA endpoints:
 - The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to day 43.

¹ There are two Versions of the HDSM-Ax: Child (9-11 years) and Adult (≥12 years). The applicant pooled data from both Versions for analysis of the endpoints.

² Day 43 is end of treatment (EOT).

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to day 43 and achieving at least a 70% reduction in GSP from baseline to day 43.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to day 43 and achieving at least a 50% reduction in GSP from baseline to day 43.

The data from Studies BBI-4000-CL-301 and BBI-4000-CL-302 demonstrated that sofipironium bromide gel, 15% had statistically significant improvement in the HDSM-Ax-7 scale scores compared to vehicle between baseline and day 43.

The HDSM-Ax — Adult and Child versions are considered two different instruments³ and were reviewed as such. Therefore, from a COA perspective, the HDSM-Ax-7 scale 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 Child version) (b) (4)

2 REVIEW CONCLUSIONS

The applicant submitted an evidence dossier for the HDSM-Ax instrument, specifically the HDSM-Ax-7 scale. The HDSM-Ax-7 scale from the HDSM-Ax — Adult and Child versions was reviewed for content validity, other measurement properties, and score interpretability (i.e., meaningful within-patient score change).

Review Summary

HDSM-Ax-7 scale from the HDSM-Ax — Adult version

- The HDSM-Ax-7 scale measures important and relevant aspects of excessive underarm sweating.
- The applicant has established content validity and the other measurement properties for the HDSM-Ax-7 scale.
- The proposed 2-point threshold for meaningful within-patient change for the HDSM-Ax-7 scale appears to be acceptable based on the applicant's anchor-based analyses. However, there is insufficient evidence to support that a 1-point threshold represents a meaningful within-patient score change in the HDSM-Ax-7 scale score.

HDSM-Ax-7 scale from the HDSM-Ax — Child version

- The applicant has provided insufficient evidence to support content validity and the other measurement properties of the HDSM-Ax-7 scale.

³ The FDA Patient-reported Outcome (PRO) Guidance (2009) describes an instrument as a means to capture data (i.e., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.

- It is unknown what constitutes a meaningful within-patient score change in the HDSM-Ax-7 scale score.

Key Issues Identified

HDSM-Ax-7 scale from the HDSM-Ax — Adult version

Issue 1: Content validity/Recall period selection

- The recall period for the HDSM-Ax-7 scale (“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.

Issue 2: Data interpretability

- The applicant pooled data from both HDSM-Ax instrument versions for analysis of the HDSM-Ax-7 scale score for the COA-related efficacy endpoints. However, the HDSM-Ax-7 scale score from the HDSM-Ax — Adult and Child versions assess different attributes of the measurement concept (severity vs. amount of sweat) and use different response options. We view the HDSM-Ax — Adult and Child versions as two different instruments and, therefore, it is inappropriate to pool data from these two instruments into a single endpoint as it limits data interpretability.
- Insufficient evidence to support a 1-point meaningful within patient change for the HDSM-Ax-7 scale score.

HDSM-Ax-7 scale from the HDSM-Ax — Child version

Issue 1: Content validity/Recall period selection

- 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 — 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 recall period for the HDSM-Ax-7 scale has limitations, which are described above in the HDSM-Ax — Adult version.

Issue 2: Other measurement properties

- Insufficient sample size to psychometrically evaluate the HDSM-Ax-7 scale score. The small sample size limits interpretation of the psychometric analyses.

Issue 3: Data interpretability

- Insufficient sample size to conduct anchor-based analyses to interpret meaningful within-patient score changes in the HDSM-Ax-7 scale score.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend that sponsors take into account additional considerations when selecting an appropriate COA for a pediatric population, including using an instrument that is content and psychometrically valid for assessment in the patient population of interest. If the concept of interest can be reliably measured across the age

spectrum of the trial patient population, we recommend using one simple version of a COA for patients of all ages in a study versus multiple versions of a COA for different age groups to avoid any unwanted measurement variability and reduce the evidentiary burden. Further, for COAs that involve a recall period, sponsors should provide supportive evidence to justify the appropriateness of the recall period to be used. The recall period should be shown to be suitable for the intended context of use (e.g., the variability, duration, frequency, and intensity of the concept measured; the disease and treatment context).

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

There have been several communications regarding the adequacy of the applicant's COA measurement strategy during the IND stage (IND 121256), which most recently included advice on the following:

- IND 121256 Type B Pre-NDA Meeting Minutes (DARRTS Reference ID: 4933828, dated February 7, 2022):
 - The Agency reiterated that HDSM-Ax-7 scale scores from the HDSM-Ax — Adult version (for patients aged ≥ 12 years) and Child version (for patients < 12 years of age) should not be pooled for psychometric evaluation, as these are distinct measure of different concepts that yield scores on different response latent scales.
- IND 121256 Information Request or Advice (DARRTS Reference ID: 4531630, dated December 10, 2019):
 - The Agency reiterated their previous comments conveyed in the Special Protocol No Agreement letter (dated January 18, 2019), stating that the proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score may not be a clinically meaningful endpoint.
 - The Agency emphasized that secondary endpoints (b) (4) need to be limited in number, clinically meaningful, and adjusted for multiplicity.
- Special Protocol Assessment dated January 18, 2019 (DARRTS Reference ID: 4378287):
 - The Agency agreed to the following:
 - The proposal of conducting two identically designed, multicenter randomized, double-blind, placebo-controlled, pivotal phase 3 studies in subjects with axillary hyperhidrosis is acceptable.
 - The co-primary efficacy endpoints of 1) the proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score (on a 0-4 score) from baseline to end-of treatment (EOT i.e., Day 43), and 2) the absolute change in gravimetric sweat production (GSP) from baseline to EOT (i.e., median of Days 41, 42 and 43) appear reasonable.
 - The proposed method to control for multiplicity using sequential testing is statistically valid.

- The Agency did not agree to the following:
 - The proposal to [REDACTED] (b) (4)
 - The proposed methods to handle missing data for the co-primary endpoints

Disease Background:

Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Primary axillary hyperhidrosis (excessive sweating without an alternative origin) is localized, characteristically symmetric, and involves the armpits. It affects approximately 4.8% of the United States (US) population (Doolittle, 2016) and is believed to be caused by an overactive cholinergic response of the sweat glands.

Investigational Product:

Sofpironium bromide, 15% drug product is a gel formulation containing sofopironium bromide drug substance for once-daily, chronic, topical application to the axillae of adult and pediatric patients with primary axillary hyperhidrosis. Following topical application and dermal absorption, sofopironium bromide exerts its therapeutic effect by selectively binding to the predominant receptor in sweat glands, thus inhibiting acetylcholine transmission and reducing sweat production.

Materials reviewed:

For regulatory materials and publications reviewed, refer to [Appendix A](#).

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies BBI-4000-CL-301 and BBI-4000-CL-302 was participants aged ≥ 9 years with a diagnosis of axillary hyperhidrosis⁴.

A complete list of the inclusion and exclusion criteria is summarized in Protocols BBI-4000-CL-301-1611 ([SDN 1](#), received date September 23, 2022) and BBI-4000-CL-302-1611 ([SDN 1](#), received date September 23, 2022).

Reviewer's comment(s):

Per the applicant, only five participants completed the HDSM-Ax — Child version across the two phase 3 studies. The sample size (n=5) was inadequate to evaluate the psychometric measurement properties of the HDSM-Ax-7 scale score from the HDSM-Ax — Child version (9-11 years). Furthermore, it was previously communicated to the applicant during the IND stage that scores on the HDSM-Ax —Adult and Child versions should not be pooled, as the two versions are considered two different instruments (DARRTS Reference ID: 4933828, dated February 7, 2022).

⁴ Diagnosis of primary axillary hyperhidrosis in the opinion of the Investigator meets all the following criteria: (1) HDSM-Ax-7 scale score of 3-4 inclusive at both of the Screening visits (Visits 1 and 4), (2) Gravimetric test indicating a minimum of 50 mg of sweat production at rest in each axilla with a two-axilla combined total of at least 150 mg of sweat production in five (5) minutes at room temperature, 20°C to 25°C (68°F to 77°F), at Screening Visit 1 and at least one of Visits 2, 3, or 4, and (3) Symptoms of axillary hyperhidrosis for ≥ 6 months' duration.

5.2 Clinical Trial Design

The applicant conducted two identical multicenter, randomized, double-blinded, vehicle-controlled phase 3 clinical trials (Studies BBI-4000-CL-301 and BBI-4000-CL-302) to evaluate safety and efficacy of topically applied sofpironium bromide gel, 15% in patients with primary axillary hyperhidrosis.

Participants were randomized 1:1 to receive sofpironium bromide gel, 15% or vehicle gel. Participants applied the investigational product once daily at bedtime to their axillae for 42 consecutive days.

5.3 Endpoint Position, Definition, and Assessment Schedule

The placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies BBI-4000-CL-301 and BBI-4000-CL-302 is summarized below.

Co-primary efficacy endpoints:

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to day 43, end-of-treatment (EOT)
- The change in gravimetrically measured sweat production (GSP) from baseline to day 43, EOT

Secondary efficacy COA endpoints:

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to day 43, 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 day 43, EOT and achieving at least a 50% reduction in GSP from baseline to EOT

The HDSM-Ax-7 was administered electronically or via paper and pencil in morning (8-10am) at Screening (Visit 1), Baseline (Day 1, Visit 4), and then every 7 days until Day 57 (Follow-up).

Reviewer's comment(s):

- *For a full list of the exploratory efficacy COA endpoints, refer to Protocols BBI-4000-CL-301- and -302.*
- *For the co-primary and secondary efficacy COA endpoints, HDSM-Ax items 1a, 1b, 2a, 2b, 2c, 2d, and 2e comprise the HDSM-Ax-7 scale score.*
- *Participants were able to complete the HDSM-Ax either via electronic and/or paper. An Agency Information Request ([SDN 14](#), received date March 24, 2023) was submitted to obtain additional details regarding the mode of administration that was used by the participants.*

- *During cognitive interviews, the interviewer did not explicitly explore the suitability of the assessment schedule of the HDSM-Ax instrument administration for capturing the variability of the patient experience with axillary hyperhidrosis. Refer to [Section 6.4](#) for explanatory quotes to highlight this point.*

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant has proposed the following specific targeted COA-related labeling claims (in *blue italicized text*):

(b) (4)



6 CLINICAL OUTCOME ASSESSMENT(S)

6.1 Clinical Outcome Assessment Description(s)

6.1.1 Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) — Adult version⁵

The HDSM-Ax — Adult version ([Appendix B](#)) 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.”

6.1.2 Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) — Child version

The HDSM-Ax — Child version ([Appendix B](#)) 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.”

Reviewer’s comment(s):

This reviewer notes that the HDSM-Ax — Adult and Child versions are considered to be two different instruments as some of the measurement concepts and response options differ. For example, the HDSM-Ax — Adult version measures severity of sweat, whereas the HDSM-Ax Child version measures the amount of sweat. For more details refer to Section 6.4 of this review

6.2 Conceptual Framework(s)

The conceptual frameworks for the HDSM-Ax — Adult and Child versions are shown in Table 1 and Table 2, respectively.

⁵Note: the COA descriptions for the HDSM-Ax are for the 11-item measure. However, the scores from the HDSM-Ax-7 Versions were used to compute the primary and secondary endpoints.

6.3 Scoring Algorithm

HDSM-Ax — Adult and Child versions

A scale score was derived from HDSM-Ax Items 1a, 1b, 2a, 2b, 2c, 2d, and 2e from both instrument versions. Because the score was derived from seven items, the scale was referred to as the HDSM-Ax-7. A mean score was calculated from the seven item responses. The mean score ranged from 0 (indicating no severity) to 4 (indicating greatest severity).

The primary analysis of the HDSM-Ax-7 co-primary endpoint will use the 2-point responder status at Day 43 (EOT). If a participant was missing any of items 1a, 1b, 2a, 2b, 2c, 2d, or 2e Visit 4 (Day 1) value, Visit 1 (Screening) value was used as Baseline. If Visit 1 (Screening) value was also missing, subject was excluded from all HDSM-Ax-7 change from baseline analyses. If a participant was missing Day 43 value, the closest (in time) available non-missing value from Day 41 (± 2 days) or Day 42 (± 2 days) was used as the first level of imputation. If none of the Days 41, 42, and 43 values were available, multiple imputations of missing EOT (i.e. Day 43) item-level scores were performed on the sofipronium bromide gel, 15% arm values using control-based imputations model. Multiple imputations assuming missing at random were performed for missing data for participants in the vehicle arm. The HDSM-Ax-7 scale score was calculated using the imputed item-level values. No other missing value imputation was performed in the coprimary analysis.

6.4 Content Validity⁶

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)

A summary of the results for each activity and instrument is described below. Refer to the applicant's PRO evidence dossier ([SDN 1](#), received date September 23, 2022) for full details regarding the methodology and results of each activity.

(b) (4)

6.5 Other Measurement Properties

The applicant evaluated the psychometric properties of the HDSM-Ax-7 scale score using data from the following studies:

- o 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.
- o Study BBI-4000-CL-301 (n= 349): refer to [Section 5.2](#) for description of clinical trial design.
- o Study BBI-4000-CL-302 (n= 347): refer to [Section 5.2](#) for description of clinical trial design.

Note that the applicant pooled the data from both HDSM-Ax — Adult and Child versions to conduct the psychometric analyses in Studies BBI-4000-CL-301 and -302. However, due to the differences in the instruments as stated above, 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 makes the data for the HDSM-Ax — Child version uninterpretable. Therefore, this section will focus on the psychometric findings the two phase 3 studies since these are the studies reported in the PRO evidence Dossier to support the use of the HDSM-Ax — Adult version, specifically the HDSM-Ax-7 scale score.

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).

The analysis population used to evaluate the measurement properties of the HDSM-Ax-7 scale score were predominantly White (>75%), non-Hispanic (>60%), and female (>55%). The mean age for Studies BBI-4000-CL-301 and BBI-4000-CL-302 reduced samples were 32.7 years (SD= 11.2) and 32.2 years (SD=11.5), respectively. For both studies, the majority of participants reported “Severe” or “Very severe” symptoms at baseline based on HDSM-Ax item 5 (severity of worst sweating) and item 6 (severity of underarm sweating over the past week).

A summary of the psychometric findings for the HDSM-Ax-7 scale score is provided below. For more details on the methodology and results of these analyses, refer to the BBI-4000-CL-301 and BBI-4000-CL-302 Phase 3 Clinical Outcome Assessment Psychometric Evaluation Reports ([SDN 1](#) and [SDN 1](#), received date September 23, 2022, respectively).

6.5.1 Item-level Descriptive Statistics

The applicant provided a description of the HDSM-Ax item scores and HDSM-Ax-7 scale score. Item score distributions were also evaluated in terms of participants’ use of the entire response scale and for floor and ceiling effects. Based on the item-level descriptive statistics:

- The majority of participants endorsed the most severe response categories for all items (i.e., category responses corresponding to a “3” [“Severe” or “Most of the time”] or “4” [“Very severe” or “All of the time”]) at baseline.

- The inter-item correlations across the items in the HDSM-Ax-7 were <0.80.
- The mean and median HDSM-AX-7 scale scores at baseline were:
 - Study BBI-4000-CL-301: 3.5 and 3.6, respectively.
 - Study BBI-4000-CL-302: 3.6 and 3.6, respectively
- The median change scores from baseline to Day 43 in the HDSM-Ax-7 are shown in Tables 3 and 4 for Studies BBI-4000-CL-301 and -302, respectively.

Table 3. Summary of median HDSM-Ax-7 scale scores at item-level at baseline, End-of-Treatment (EOT), and change from baseline in the Study BBI-4000-CL-301(Reduced Sample).

HDSM-Ax-7	Vehicle (n= 177)			SB Gel 15% (n= 172)		
	Baseline (n=177)	EOT* (n=166)	Change from baseline	Baseline (n=172)	EOT* (n=156)	Change from baseline
1a. How often wet clothes underarm sweating	4.0	2.0	-1.0	4.0	1.0	-2.0
1b. How often underarm sweating for no reason	4.0	2.0	-1.0	4.0	1.0	-2.0
2a. How much underarm sweating when nervous	4.0	2.0	-1.0	4.0	2.0	-2.0
2b. How much wet clothing	4.0	2.0	-2.0	3.0	1.0	-2.0
2c. How much underarm sweating-no exercise	3.0	2.0	-1.0	3.0	1.0	-2.0
2d. How much underarm wetness	4.0	2.0	-2.0	3.0	1.0	-2.0
2e. How much underarm sweating no reason	4.0	2.0	-2.0	3.0	1.0	-2.0

*End of Treatment (EOT) for HDSM-Ax was Visit 12 (Day 43), if non-missing. If Visit 12 was missing, EOT was the closest available non-missing value at Visit 10 (Day 41) or Visit 11 (Day 42).

Note: Baseline is the HDSM-Ax-7 item score at Visit 4.

Source: BBI-4000-CL-301 - Table IR10.1.1.301, [SDN 16](#), received date May 9, 2023.

Table 4. Summary of median HDSM-Ax-7 scale scores at item-level at baseline, End-of-Treatment (EOT), and change from baseline in the Study BBI-4000-CL-302 (Reduced Sample).

HDSM-Ax-7	Vehicle (n= 169)			SB Gel 15% (n= 178)		
	Baseline (n=169)	EOT* (n=157)	Change from baseline	Baseline (n=178)	EOT* (n=160)	Change from baseline
1a. How often wet clothes underarm sweating	4.0	2.0	-2.0	4.0	1.0	-2.0
1b. How often underarm sweating for no reason	4.0	2.0	-2.0	4.0	1.0	-2.0
2a. How much underarm sweating when nervous	4.0	2.0	-2.0	4.0	1.0	-2.0
2b. How much wet clothing	4.0	2.0	-2.0	4.0	1.0	-2.0
2c. How much underarm sweating-no exercise	4.0	2.0	-2.0	4.0	1.0	-2.0
2d. How much underarm wetness	4.0	2.0	-2.0	4.0	1.0	-2.0
2e. How much underarm sweating no reason	4.0	2.0	-2.0	4.0	1.0	-2.0

*End of Treatment (EOT) for HDSM-Ax was Visit 12 (Day 43), if non-missing. If Visit 12 was missing, EOT was the closest available non-missing value at Visit 10 (Day 41) or Visit 11 (Day 42).

Note: Baseline is the HDSM-Ax-7 item score at Visit 4.

Source: BBI-4000-CL-302-Table IR10.1.1.302, [SDN 16](#), received date May 9, 2023.

Reviewer's comment(s):

- In response to FDA Information Requests (IRs) dated March 20, 2023, and May 3, 2023, the Applicant provided item-level descriptive statistics by each study visit for the HDSM-Ax-7 scale score for each study by the different instrument Versions. However, the Sponsor did not include descriptive statistics for the scale score.
- The applicant indicated that higher (more severe) scores at baseline is an expected observable pattern considering that participants who enter a clinical trial tend to have a more severe clinical presentation. The hope was that scores would decrease in response to treatment, representing lesser symptom severity or symptom resolution. Clinical previously agreed to a higher level of severity at baseline and reiterated that the sponsor's, "...trial should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity..." (p. 12 of 15, DARRTS Reference ID: 3470432, dated March 13, 2014).

- *The Agency also communicated to the applicant that severity and duration of sweat production are both relevant for assessing efficacy and noted that relative importance of the two attributes may change by including more questions on severity or duration compared to the other (p. 14 of 23, DARRTS Reference ID: 4218179, dated February 7, 2018).*
- *The inter-item correlations for the items within the HDSM-Ax-7 scale score were less than 0.80, which suggests that there is no measurement redundancy across the items.*

6.5.2 Dimensionality Analyses

Dimensionality analyses were conducted to evaluate the relationship between the HDSM-AX-7 items and scale score, as well as the appropriateness of summing the items into a scale score. Based on the dimensionality analyses:

- For both studies, corrected item-scale correlations were weak to moderate at baseline ($0.35 < r < 0.67$) but improved to strong and very strong at Day 15 ($0.89 < r < 0.95$) and Day 43 ($0.94 < r < 0.96$).
- For both studies, the first factor across all three timepoints (Baseline, Day 15, and Day 43) stood out from the subsequent six factors.
 - Study BBI-4000-CL-301: The eigenvalues of the first factor was 2.30 at Baseline, 5.77 at Day 15, and 6.04 at Day 43. The eigenvalues of the subsequent six factors level out between 0.24 and -0.25.
 - Study BBI-4000-CL-302: The eigenvalues of the first factor was 2.22 at Baseline, 5.89 at Day 15, and 6.19 at Day 43). The eigenvalues of the subsequent six factors level out between 0.12 and -0.21.
- For the confirmatory factor analysis, the model fit statistics for the HDSM-Ax-7 (unidimensional model) were as follows across the three timepoints:
 - Study BBI-4000-CL-301: Comparative Fit Index (CFI) ≥ 0.90 , root-mean-square error of approximation (RMSEA) ranged from 0.054 to 0.122, and modification indices¹² > 10 for some item pairs (baseline: items 1a and 1b, items 1a and 2a, and 1a and 2e; Day 15: items 1a and 1b).
 - Study BBI-4000-CL-302: CFI ≥ 0.90 , RMSEA ranged between 0.045 and 0.083, and modification indices¹² > 10 for some item pairs (baseline: items 1a and 1b; Day 15: items 1a and 1b).
 - Factor loadings, which measure the correlation between item responses and the latent construct, were above 0.90 at Day 15 and Day 43.

Reviewer's comment(s):

- *Stronger correlations conveyed that item scores appear adequately related to total scores.*
- *Note that there was an inclusion criterion for Studies BBI-4000-CL-301 and -302 that enrolled participants with an HDSM-Ax-7 scale score of 3-4 inclusive at both of the Screening visits (Visits 1 and 4).*
- *Based on the eigenvalue analysis, it appears that one domain may be sufficient for the HDSM-Ax-7 scale score.*

¹² Lagrange multiplier statistics

- *This reviewer notes that for Study BBI-4000-CL-301 there were conflicting results in which RMSEA at baseline showed inadequate model fit (> 0.10) while CFI showed good model fit (> 0.90). The Applicant indicated that this result is common when participants who are similar in severity yield responses that do not utilize the full range of the response scale. However, the results were consistent for Study BBI-4000-CL-302 despite participants having similar severity levels at baseline.*
- *The modification indices identified some potentially misfitting item pairs, particularly HDSM-Ax items 1a and 1b.*

6.5.3 Reliability

6.5.3.1 Internal consistency reliability

Internal consistency reliability analyses were conducted to evaluate whether all the items in the HDSM-Ax-7 scale score were measuring severity and frequency of excessive underarm sweating as intended. Based on the internal consistency reliability analyses,

- Cronbach's α for the HDSM-Ax-7 scale score was >0.70 at all-time points.
 - o Study BBI-4000-CL-301: Cronbach's α ranged from 0.756 at Baseline to 0.977 at Day 43.
 - o Study BBI-4000-CL-302: Cronbach's α ranged from 0.756 at Baseline to 0.982 at Day 43.

6.5.3.2 Test-retest reliability

Test-retest reliability analyses were conducted to assess whether the scores are reasonably consistent over time within clinically stable¹³ patients. Based on the test-retest reliability analyses,

- Study BBI-4000-CL-301: The intra-class correlation coefficient (ICC)¹⁴ estimate for the analysis population defined by the HDSM-Ax-7 scale scores at Screening and Baseline was 0.631. The ICC estimate for the analysis population defined by the Patient Global Impression of Severity (PGI-S; underarm sweating) response at Days 41 and 43 was 0.948.
- Study BBI-4000-CL-302: The ICC estimate for the HDSM-Ax-7 scale scores at Screening and Baseline was 0.694. The ICC estimate for the analysis population defined by the PGI-S response at Days 41 and 43 was 0.940.

Reviewer's comment(s):

An IR was sent to the Applicant on June 15, 2023, requesting additional test-retest reliability analyses using an alternative analysis population (i.e., patients who reported the same response on the Patient Global Impression of Severity (PGI-S; underarm sweating) item at Screening and Baseline. For Studies BBI-4000-CL-301 and -302, the ICC estimates

¹³ Stability was defined using different approaches: (1) Participants who completed the HDSM-Ax — Adult version with non-missing HDSM-Ax-7 total scores at both the Screening and Baseline visits, (2) Participants who completed the HDSM-Ax — Adult version with non-missing HDSM-Ax-7 total scores at Day 41 through Day 43, and (3) Participants who had the same PGI-S response at Day 41 and Day 43.

¹⁴ McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. *Psychological Methods*. 1996;1(1):30-46.

for participants with the same PGI-S response at Screening and Baseline were 0.631 and 0.694, respectively.

While the ICC estimates fall below acceptable range for some of the analysis populations (i.e., participants with non-missing HDSM-Ax-7 scale scores at Screening and Baseline and same PGI-S response at Screening and Baseline), this could be a result of 1) the variability of axillary hyperhidrosis symptoms and/or (2) the analysis population may not be clinically stable at the specified timeframe. This reviewer notes that the timeframe between Screening and Baseline visits was no more than 31 days to Visit 2 then Visit 3 and Visit 4 within 14 days of baseline (Visit 4). The separation between these two specified timepoints (Screening and Baseline) may be too far apart which may also have had an impact on the results of the test-retest reliability analyses. This reviewer notes that the ICC estimates fall within acceptable and reasonable range for the analysis population defined by the PGI-S responses at Days 41 and 43. This could be a result of the close time proximity between Days 41 and 43 (i.e., symptom fluctuation may have been minimal). The general recommendation for selection of time points for test-retest reliability is that they should not be too distant to ensure reproducible results nor too close together to mitigate any potential carry-over effect (e.g., learning effect).

6.5.4 Construct Validity

6.5.4.1 Convergent and Divergent Validity

Convergent validity and divergent validity were evaluated via correlation analyses to examine the associations between concepts measured by the HDSM-Ax-7 scale score and concepts measured by other instruments and whether these concepts correlate with one another as expected. The reference instruments used included: gravimetric sweat production (GSP), Dermatology Quality Life Index (DQLI) total score, PGI-S (underarm sweating), and HDSM-Ax-7 Items 4 (underarm sweating frequency) and item 5 (underarm sweating severity).

Based on the correlation analyses¹⁵,

- Study BBI-4000-CL-301:
 - Weak to strong correlations were observed between the mean HDSM-Ax-7 scale scores and the GSP ($r = 0.22 - 0.45$) and DLQI total score ($0.33 - 0.73$) at Baseline, Day 15, and Day 43.
 - Moderate to very strong correlations were observed between the mean HDSM-Ax-7 scale scores and the PGI-S ($r = 0.66 - 0.94$), HDSM-Ax Item 4 (underarm sweating frequency) ($r = 0.60 - 0.95$), and HDSM-Ax Item 5 (underarm sweating severity) ($0.53 - 0.95$) at Baseline, Day 15, and Day 43.
- Study BBI-4000-CL-302:
 - Weak to moderate correlations were observed between the mean HDSM-Ax-7 scale scores and the GSP ($r = 0.23 - 0.37$) and DLQI total score ($r = 0.27 - 0.68$) at Baseline, Day, and Day 43.

¹⁵ Spearman and polyserial coefficients were reported with their 95% CIs (interpreted as 0.00 to 0.30=weak, 0.31 to 0.70=moderate, 0.71 to 0.90=strong, and 0.91 to 1.00=very strong relationships).

- o Moderate to very strong correlations ($r=0.59-0.94$) were observed between the mean HDSM-Ax-7 scale scores and the PGI-S ($r= 0.74 - 0.94$), HDSM-Ax Item 4 (underarm sweating frequency) ($r= 0.59 - 0.95$), and HDSM-Ax Item 5 (underarm sweating severity) ($r= 0.61 - 0.93$) at Baseline, Day 15, and Day 43.

Reviewer's comment(s):

The applicant indicates that the observed correlations were expected:

- *The hypothesized relationship between the HDSM-Ax-7 scale score and GSP was weak.*
- *The hypothesized relationships between the HDSM-Ax-7 scale score and other measures were moderate.*

This reviewer notes that the GSP, PGI-S (underarm sweating), and HDSM-Ax-7 items 4 and 5 appear to measure similar concepts (convergent validity) of the HDSM-Ax-7 scale score as they are related to aspects of underarm sweating. However, the objective of GSP is to quantitate sweat production which does not provide information regarding sweat severity and/or frequency, which may be a reason why the hypothesized relationship between this measure and HDSM-Ax-7 scale score was weak. The concepts measured in the DLQI total score are somewhat dissimilar (divergent validity) to the HDSM-Ax-7 scale score as it measures generic skin symptoms and impacts and not specific to underarm sweating.

6.5.4.2 Known-Groups Validity

The following patient-reported assessments were used to conduct empirical comparisons of scores for patient groups expected to differ with respect to underarm sweating:

1. HDSM-Ax Item 4: sweating frequency in the past 24 hours
2. HDSM-Ax Item 5: sweating severity in the past 24 hours, and
3. HDSM-Ax Item 6 and PGI-S: sweating severity in the past week

Based on the known-groups validity analyses, for both studies (Study BBI-4000-CL-301 and -302 (reduced sample)) the HDSM-Ax-7 mean and median values increased in all cases in concert with the pre-defined severity grouping at each timepoint (Baseline, Day 15, and Day 43).

Reviewer's comment(s):

- *The applicant reported that the results showed statistically significant p-values and no overlap in the 95% confidence intervals for the medians. Note that the applicant did not provide box plots.*
- *The HDSM-Ax-7 scale score observed across the patient-reported assessments showed better scores (lower scores) on average for patient subgroups with no/mild sweating and occurrence of sweat at none of the time/little of the time at each timepoint. As such, the HDSM-Ax-7 appears to be able to differentiate between clinically distinct groups.*

6.5.5 Responsiveness (ability to detect change)

Responsiveness was evaluated via the effect size (Cohen's d)¹⁶ and correlation analyses.

Based on these analyses:

- Study BBI-4000-CL-301:
 - o The effect size for the HDSM-Ax-7 scale score at Days 15 and 43 were -3.52 (-4.91, -2.12) and -5.24 (-6.63, -3.84), respectively.
 - o The correlation of change scores in the HDSM-Ax-7 scale score and reference measures are shown in Table 5.

Table 5. Correlations of changes in HDSM-Ax-7 scale scores with supplementary measure scores between Baseline and Day 43

Supplementary measure	Type	Estimate (95% CI)
Change in sweating frequency (HDSM-Ax Item 4) ^[1] (N=316)	Polyserial	0.89 (0.86–0.91)
Change in sweating severity (HDSM-Ax Item 5) ^[2] (N=316)	Polyserial	0.88 (0.85–0.90)
Change in PGI-S (HDSM-Ax Item 6) ^[3] (N=316)	Polyserial	0.86 (0.83–0.89)
PGI-C (HDSM-Ax Item 7) ^[4] (N=316)	Polyserial	0.77 (0.72–0.81)
Change in DLQI total score ^[5] (N=297)	Spearman	0.33 (0.23–0.43)
Change in GSP ^[6] (N=313)	Spearman	0.26 (0.15–0.36)

Source: Table 27 in BB8705A CL-301R Psych Eval Report 1b Reduced Sample v2_0

- Study BBI-4000-CL-302:
 - o The effect size for the HDSM-Ax-7 scale score at Days 15 and 43 were -4.33 (-5.72, -2.93) and -6.13 (-7.53, -4.74), respectively.
 - o The correlation of change scores in the HDSM-Ax-7 scale score and reference measures are shown in Table 6.

Table 6. Correlations of changes in HDSM-Ax-7 scale scores with supplementary measure scores between Baseline and Day 43 (n=316)

Supplementary measure	Type	Estimate (95% CI)
Change in sweating frequency (HDSM-Ax Item 4) ^[1] (N=313)	Polyserial	0.89 (0.86–0.91)
Change in sweating severity (HDSM-Ax Item 5) ^[2] (N=313)	Polyserial	0.89 (0.87–0.91)
Change in PGI-S (HDSM-Ax Item 6) ^[3] (N=313)	Polyserial	0.89 (0.86–0.91)
PGI-C (HDSM-Ax Item 7) ^[4] (N=313)	Polyserial	0.75 (0.70–0.80)
Change in DLQI total score (adults only) ^[5] (N=297)	Spearman	0.50 (0.41–0.58)
Change in GSP ^[6] (N=307)	Spearman	0.29 (0.18–0.39)

Source: Table 27 in BB8705A CL-302R Psych Eval Report 2b Reduced Sample v2_0

Reviewer's comment(s): Generally, for assessment of responsiveness, sponsors should provide the distribution of change on the target instrument by change on each anchor by providing descriptive statistics for improvement in the target instrument for each level of categorical improvement in the anchors [N (total number), mean, median, standard deviation, range, and confidence intervals]. This applicant did conduct this analysis; however, it was conducted as part of the anchor-based analyses (refer to Section 6.6). The distribution-based method (i.e., effect size) provides supportive evidence of responsiveness.

¹⁶ Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York: Taylor Francis; 2013.

6.6 Interpretation of Meaningful Within-Patient Score Changes

6.6.1 HDSM-Ax – Adult Version

The applicant proposed that a 2-point reduction (improvement) in the HDSM-AX-7 scale score from baseline to Day 43 (EOT) represents a clinically meaningful within-patient score change. To support this threshold of clinically meaningful within patient change, the applicant performed the following analyses using data from Studies BBI-4000-CL-301 and -302:

- Anchor-based analyses
 - Distribution of change on the target COAs by change on anchors
 - Anchor-based empirical cumulative distribution function (eCDF) and probability density function (PDF) curves

Table 7 summarizes the anchors scales utilized by the applicant and their corresponding target COA. Copies of the anchor scales are in [Appendix C](#).

Table 7. Timing of COA Endpoint and Anchor Scales for Studies BBI-4000-CL-301 and -302.

Endpoint concept/attribute (COA type/name if any)	Anchor (concept)	Anchor response scale	Recall period (target/anchor)	Timing of COA endpoint (target/anchor)
HDSM-Ax-7 scale score (underarm sweating severity and frequency)	PGI-S* (underarm sweating severity)	5-point VRS: None, Mild, Moderate, Severe, Very severe	Since you woke up yesterday/ Past week (7-days)	Day 43 (EOT)/ Day 43 (EOT)
	PGI-C* (underarm sweating)	7-point VRS: Very much better, Moderately better, A little better, No change, A little worse, Moderately worse, Very much worse	Since you woke up yesterday) / comparison of current state to earlier period (“since you started taking the study medication”)	Day 43 (EOT)/ Day 43 (EOT)
	HDSM-Ax Item 4 (underarm sweating frequency)	5-point VRS: None of the time, A little of the time, Some of the time, Most of the time, All of the time	Since you woke up yesterday/Since you woke up yesterday	Day 43 (EOT)/ Day 43 (EOT)
	HDSM-Ax Item 5 (underarm sweating severity)	5-point VRS: I did not have underarm sweating (i.e., completely dry), I had underarm sweating, but it was mild (i.e., slightly damp), I had underarm sweating, and it was moderate (i.e., damp), I had underarm sweating, and it was severe (i.e., wet), I had underarm sweating, and it was very severe (i.e., soaking)	Since you woke up yesterday/Since you woke up yesterday	Day 43 (EOT)/ Day 43 (EOT)

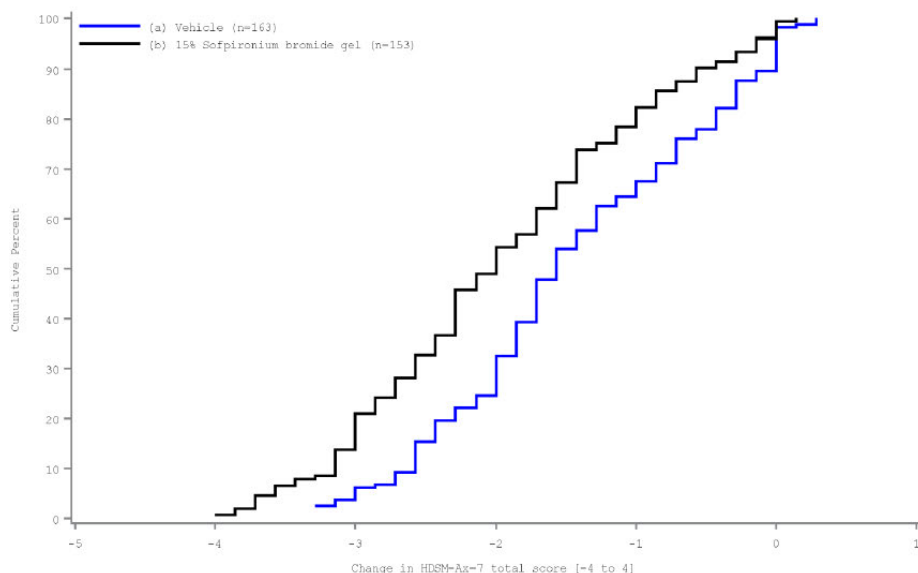
Abbreviations: HDSM-Ax= Hyperhidrosis Disease Severity Measure-Axillae; PGI-C= Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; EOT= end of treatment; FU= follow-up; VRS= verbal rating scale.

*PGI-S was administered as Question #6 of HDSM-Ax at every assessment; PGI-C will be administered as Question #7 of HDSM-Ax at the Day 43 visit only for Studies 301 and 302.

While the applicant conducted additional anchor-based analyses, the Agency previously 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) based on the SPA correspondence dated January 18, 2019 (DARRTS Reference ID: 4378287) during the IND phase. Refer to [Section 4](#) of this review for more details. As such, this section does not present the results from the anchor-based analyses. Refer to the PRO evidence dossier for details on the methodology and results of these analyses.

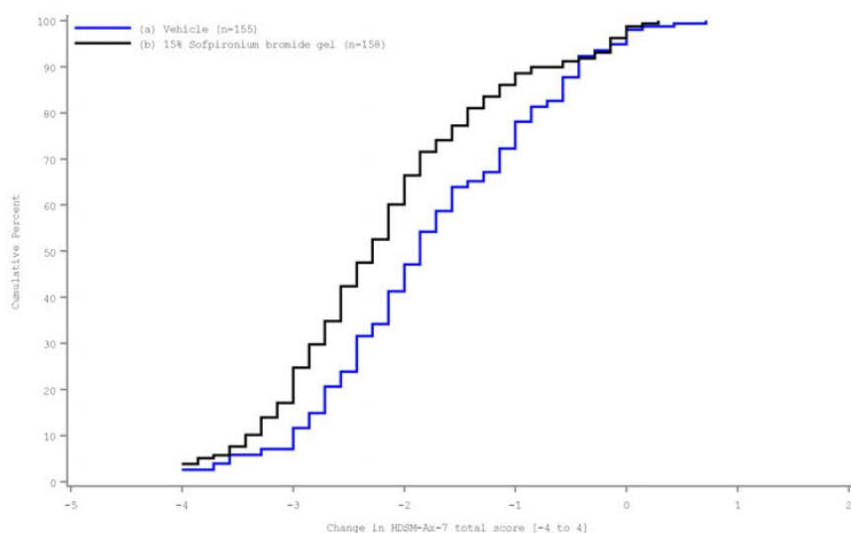
Reviewer's comment(s):

- *It was previously communicated to the applicant (DARRTS Referend ID: 4933828, dated February 7, 2022) that the misalignment between the PGI-S anchor and the instrument would make it challenging to interpret the data generated from the anchor-based analyses.*
- *The applicant included HDSM-Ax items 4 (underarm sweating frequency) and 5 (underarm sweating severity) from the HDSM-Ax instrument to aid in the interpretation of clinically meaningful within patients change in addition to the PGIS and PGIC anchor scales (IND 121256, SDN 72, received date October 19, 2018).*
- *Per the SPA No-Agreement letter dated January 18, 2019, the applicant still has not provided sufficient evidence to support whether at least a 1-point improvement in the HDSM-Ax-7 scale score is a clinically meaningful endpoint to patients with primary axillary hyperhidrosis based on their phase 2 data.*
 - *The applicant provided insufficient evidence to support a 1-point meaningful within patient change for the HDSM-Ax-7 scale score. For example, there appears to be overlap between no change and a 1-point change on the PDF curves for the reduced samples for Studies BBI-4000-CL-301 and -302. Furthermore, the eCDF curves appear to have overlap between the no change and a 1-point change (a little better) curves for Studies BBI-4000-CL-301 and -302- whereas the 2-point change (moderately better) appears more distinct and separate from the other curves.*
- *The applicant did not include CDF curves by treatment arm (treatment vs. vehicle) in their PRO evidence dossier for the reduced sample from Studies BBI-4000-CL-301 and -302. However, this information was found in the individual reduced sample reports for Studies BBI-4000-CL-301 and 302 (see Figures 4 and 5 below).*

Figure 1. Cumulative distribution function for change in HDSM-Ax-7 total score by treatment from baseline to visit 12 (Study 301 reduced sample).

Note: The PsAP1r consists of ITT patients enrolled in the BBI-4000-CL-301 study with at least one non-missing item response to the adult version of the HDSM-Ax at baseline, visit 6, or visit 12.
 Note: The HDSM-Ax-7 total score ranges from 0-4 with higher scores indicating greater severity. Negative change scores are indicative of improvement.

Source: Sponsor's BBI-4000-CL-301- Psychometric Evaluation Report 1b (Reduced Sample) - PRO Report BB8705A, Figure 7.1 (p. 543 of 554, [SDN 1](#), received date September 23, 2022).

Figure 2. Cumulative distribution function for change in HDSM-Ax-7 total score by treatment from baseline to visit 12 (Study 301 reduced sample).

Note: The PsAP2r consists of ITT patients enrolled in the BBI-4000-CL-302 study with at least one non-missing item response to the adult version of the HDSM-Ax at baseline, visit 6, or visit 12.
 Note: The HDSM-Ax-7 total score ranges from 0-4 with higher scores indicating greater severity. Negative change scores are indicative of improvement.

Source: Sponsor's BBI-4000-CL-302- Psychometric Evaluation Report 2b (Reduced Sample) - PRO Report BB8705A, Figure 7.1 (p. 543 of 554, [SDN 1](#), received date September 23, 2022).

6. APPENDICES

Appendix A: Regulatory Materials and Publications Reviewed

Document	SDN	eCTD#	Date Received
1.12.4 IND 121256 Request for Comments - HDSM-Ax PRO Analysis Rpt	21	0017	14Jun2016
1.11.3 IND 121256 Clinical Information Amendment - Responses to FDA Comments	72	0068	19Oct2018
1.8.1 Request for Special Protocol Assessment Phase 3 Pivotal Study Protocol for Sofpironium Bromide Gel for Treatment of Primary Axillary Hyperhidrosis	77	0073	07Dec2018
1.11.3 Clinical Information Amendment - Response to SPA Comments	85	0081	10May2019
1.11.3 Clinical Information Amendment - Response to FDA Advice Letter and Request for Information	94	0089	20Sep2019
1.11.3 IND 121256 Serial No. 0033 - Attachment 1: Qualitative Research Report 19May2017	1	0001	23Sep2022
16.1.9 BBI-4000-CL-301 - 16.1.9 Documentation of Statistical Methods	1	0001	23Sep2022
16.1.9 BBI-4000-CL-302 - 16.1.9 Documentation of Statistical Methods	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0033 - Attachment 2: Patient Interview Transcripts	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0033 - Attachment 3: HDSM-Ax: CTT and RMT Scoring Text	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0033 - Attachment 4: HDSM-Ax: CTT and RMT Scoring Equations	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0047 - Clinical Information Amendment	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0059 05/31/2018- Clinical Information Amendment - Response to FDA Type C Meeting WRO	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0068 10/19/2018 - Clinical Information Amendment - Response to FDA Comments	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0081 05/10/2018- Clinical Information Amendment - Response to SPA Comments	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0089 09/20/2019- Clinical Information Amendment - Response to FDA Advice Letter and Request for Information	1	0001	23Sep2022
1.11.3 IND 121256 Serial No. 0093 01/24/2020 - Clinical Information Amendment - Response to FDA Advice Letter and Request for Information	1	0001	23Sep2022
1.11.3 - Clinical Information Amendment - Studies BBI-4000-CL-301 12/06/2022	4	0004	06Dec2022
5.3.5.4 HDSM-Ax - Patient Report Outcome Dossier for BBI-4000-CL-301 and BBI-4000-CL-302 (PRO Dossier) 18Jul2022	1	0001	23Sep2022
5.3.5.4 HDSM-Ax - Summary of Measure Development and Content Validity Evidence 12Feb2015	1	0001	23Sep2022
5.3.5.4 HDSM-Ax - Content Development and Psychometric Testing: Summary of Methods and Results 30May2016	1	0001	23Sep2022
5.3.5.4 HDSM-Ax - Report of Findings: Cognitive Debriefing of Adolescent Participants (Ages 9-17) 27Apr2017	1	0001	23Sep2022

5.3.5.4 HDSM-Ax - BB8705A Psychometric Analysis Plan 02May2022	1	0001	23Sep2022
5.3.5.4 HDSM-Ax - Qualitative Research Summary Report 19May2017	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-301-2 Synopsis	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-302-2 Synopsis	1	0001	23Sep2022
16.1.1 BI-4000-CL-301- 16.1.1 Protocol and Protocol Amendments	1	0001	23Sep2022
16.1.1 BI-4000-CL-302- 16.1.1 Protocol and Protocol Amendments	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-301- Psychometric Evaluation Report 1a (Full Sample) - PRO Report BB8705A	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-301- Psychometric Evaluation Report 1b (Reduced Sample) - PRO Report BB8705A	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-302- Psychometric Evaluation Report (Full Sample) - PRO Report BB8705A	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-302- Psychometric Evaluation Report (Reduced Sample) - PRO Report BB8705A	1	0001	23Sep2022
5.3.5.1 BBI-4000-CL-301 - Table IR8.1.301	14	0014	24Feb2023
5.3.5.1 BBI-4000-CL-301 - Table IR8.2.301	14	0014	24Feb2023
5.3.5.1 BBI-4000-CL-301 - Listing IR8.2.301	14	0014	24Feb2023
5.3.5.1 BBI-4000-CL-302 - Table IR8.1.302	14	0014	24Feb2023
5.3.5.1 BBI-4000-CL-302 - Table IR8.2.302	14	0014	24Feb2023
5.3.5.1 BBI-4000-CL-302 - Listing IR8.2.302	14	0014	24Feb2023
1.11.3 Clinical Information Amendment - Response to Information Requested dated March 20, 2023	14	0014	24Mar2023
5.3.5.4 HDSM-Ax - US Cognitive Debriefing Study Report 26April2019	14	0014	24Mar2023
5.3.5.1 BBI-4000-CL-302-Table IR10.1.1.302	16	0016	09May2023
5.3.5.1 BBI-4000-CL-301 - Table IR10.1.1.301	16	0016	09May2023
1.11.3 Clinical Information Amendment - Response to Information Request dated May 03,2023	16	0016	09May2023
1.11.3 Clinical Information Amendment - Response to Information Request dated June 15, 2023	18	0018	23Jun2023
5.3.5.1 BBI-4000-CL-203 - 2 Synopsis	1	0001	23Sep2023
1.6.3 Sponsor Response to FDA EOP2 Meeting comments 02/18/2022	1	0001	23Sep2023
Communications and Reviews	DARRTS Ref ID	Date	
C2021459 IND 121256 DCOA Consult Memorandum_Choudhry	4924475	07Mar2022	
IND 121256 Type B Pre-NDA Meeting Minutes	4933828	07Feb2022	
IND 121256 Special Protocol Assessment No Agreement	4378287	18Jan2019	
IND 121256 Information Request or Advice	4457983	03Jul2019	
IND 121256 Information Request or Advice	4531630	10Dec2019	
C2018324 IND 121256 DCOA Consult Memorandum_Campbell	4357201	10Dec2018	
C2018161 IND 121256 DCOA Consult Memorandum_Campbell	4295363	23Jul2018	
C2018047 IND 121256 DCOA Consult Memorandum_Campbell	4256448	01May2018	

C2018078 IND 121256 DCOA Consult Memorandum_Campbell	4404019	14Mar2018
C2017159 IND 121256 DCOA Consult Memorandum_Campbell	4124714	13Aug2017
IND 121256 Information Request or Advice	4037116	05Jan2017
AT2016-135 IND 121256 DCOA Consult Memorandum_Campbell	4021792	14Dec2016
PIND 121256 Final Meeting Minutes	3470432	13Mar2014
Publications		
1. Vorkamp T, Foo FJ, Khan S, Schmitto JD, Wilson P. Hyperhidrosis: evolving concepts and a comprehensive review. <i>Surgeon</i>. 2010;8(5):287-292. 2. Solish N, Bertucci V, Dansereau A et al. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. <i>Dermatol Surg</i>. 2007;33(8):908-923. 3. Schlereth T, Dieterich M, Birklein F. Hyperhidrosis--causes and treatment of enhanced sweating. <i>Dtsch Arztebl Int</i>. 2009 Jan;106(3):32-7. 4. Haider A, Solish N. Focal hyperhidrosis: diagnosis and management. <i>CMAJ</i>. 2005 Jan 4 5. Walling HW, Swick BL. Treatment options for hyperhidrosis. <i>Am J Clin Dermatol</i>. 2011 Oct 1;12(5):285-95. 6. Strutton DR, Kowalski JW, Glaser DA, Stang PE. US prevalence of hyperhidrosis and impact on individuals with AHH: results from a national survey. <i>J Am Acad Dermatol</i>. 2004;51(2):241-248. 7. Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. <i>Arch Dermatol Res</i>. 2016; 308(10):743-749.		

Appendix B: Copies of COAs

Figure 3. Hyperhidrosis Disease Severity Measure-Axillary –Adult version (HDSM-Ax; ≥12 years of age)

**Hyperhidrosis Disease Severity Measure-Axillary® ≥12 Years of Age
(HDSM-Ax) (version 1.3)**

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 <u>underarm sweating</u> ?	0	1	2	3	4
b) <u>Underarm sweating</u> 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) <u>Underarm sweating</u> when you felt nervous, stressed or anxious?	0	1	2	3	4
b) Damp or wet clothing caused by <u>underarm sweating</u> ?	0	1	2	3	4
c) <u>Underarm sweating</u> after little or no physical exercise?	0	1	2	3	4
d) <u>Underarm</u> wetness?	0	1	2	3	4
e) <u>Underarm sweating</u> for no apparent reason?	0	1	2	3	4
f) <u>Underarm sweating</u> that was unmanageable?	0	1	2	3	4
g) <u>Underarm sweating</u> 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 <u>underarm sweating</u> ?	0	1	2	3	4
b) Feeling the need to wipe sweat from your <u>underarms</u> ?	0	1	2	3	4

NOTE: Only items 1a, 1b, 2a, 2b, 2c, 2d, and 2e comprise the HDSM-Ax-7, which was used to support efficacy labeling claims.

Figure 4. Hyperhidrosis Disease Severity Measure-Axillary — Child version (HDSM-Ax; ≥ 9 to <12 years of age)

Hyperhidrosis Disease Severity Measure-Axillary, Child (≥ 9 to <12 years of age)
HDSM-Ax Child (version 28 FEB 2018)

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 clothing from <u>underarm sweating</u> ?	0	1	2	3	4
b) <u>Underarm sweating</u> 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) <u>Underarm sweating</u> when you felt nervous, scared, or worried?	0	1	2	3	4
b) Damp or wet clothing from <u>underarm sweating</u> ?	0	1	2	3	4
c) <u>Underarm sweating</u> after sitting quietly?	0	1	2	3	4
d) <u>Underarm wetness</u> ?	0	1	2	3	4
e) <u>Underarm sweating</u> for no reason?	0	1	2	3	4
f) <u>Underarm sweating</u> that you could not hide?	0	1	2	3	4
g) <u>Underarm sweating</u> 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 <u>underarm sweating</u> ?	0	1	2	3	4
b) Wipe sweat from your <u>underarms</u> ?	0	1	2	3	4

NOTE: Only items 1a, 1b, 2a, 2b, 2c, 2d, and 2e comprise the HDSM-Ax-7, which was used to support efficacy labeling claims.

Appendix C: Copies of Anchor Scales

Figure 5. Sweating frequency item (HDSM-Ax Item 4)

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 |

Figure 6. Sweating severity item (HDSM-Ax Item 5)

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 <u>mild</u> (i.e., slightly damp) |
| 2 | I had underarm sweating and it was <u>moderate</u> (i.e., damp) |
| 3 | I had underarm sweating and it was <u>severe</u> (i.e., wet) |
| 4 | I had underarm sweating and it was <u>very severe</u> (i.e., soaking) |

Figure 7. Patient Global Impression of symptom severity (PGI-S)**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 |

Figure 8. 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

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/

SELENA R DANIELS
09/18/2023 03:12:35 PM

DAVID S REASNER
09/18/2023 04:03:37 PM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis [1](#) (DMEPA [1](#))

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 15, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217347
Drug Constituent Name and Strength	sofipironium bromide topical gel, 15%
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Multi-Dose Metered Pump
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Botanix SB, Inc. (Botanix)
FDA Received Date:	September 23, 2022 & February 17, 2023
OSE RCM #:	2022-1832
DMEPA 1 Human Factors Evaluator:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors (Acting) & Deputy Director:	Jason Flint, MBA, PMP
DMEPA 1 Division Director:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

Botanix submitted a New Drug Application (NDA) for their proposed sofpironium bromide topical gel drug product on September 23, 2022, under NDA 217347. This is a combination product with a proposed airless multi-dose metered pump device constituent part that is intended for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.

1.1 PRODUCT DESCRIPTION

The proposed device is an airless metered pump. The product is multi-dose with a full dose dispensed with each pump. The product carton comes with one pump and dose applicator and the instructions for use (IFU). See figures 1 and 2 below.

Figure 1: Proposed Product (pump [left], applicator [center], cap [right])

Figure 2: Carton with IFU

(b) (4)

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On November 19, 2021, the Applicant submitted a human factors (HF) validation study protocol, and we provided our review and feedback on January 10, 2022^a. The Sponsor submitted HF validation study results on September 23, 2022, which is the focus of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

^a Oguntimein, O. HF Validation Study Protocol Review for sofipirionium bromide (IND 121256). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2021-2263.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• Adult patients who have been diagnosed with axillary hyperhidrosis or experience excessive sweatiness in general (ages 18+ years old) [n=15] • Pediatric patients who have been diagnosed with axillary hyperhidrosis or experience excessive sweatiness in general (ages 9-17 years old) [n=15] • Adult caregivers who provide general care to adult or pediatric lay users or who formally provide care (ages 18+ years old) [n=15]
Training	All participants were untrained.
Test Environment	Study sessions took place in a controlled usability lab environment, designed to simulate a real-world home environment. The usability lab was configured with a table and chairs for the research participant and study moderator. A functional sink was available for use in the room to allow participants to simulate handwashing or rinsing tasks, as needed. For the caregiver user group, a manikin was seated in a chair.

	Environment Variables	Description	
		Intended Use Environment	Simulated Use Environment
	Location	Home use	Usability lab set up to represent a home bathroom environment
	Noise and Distraction	Some level of noise and distraction is expected. Variable noise from quiet (40 dB) to loud (80 dB)	Standard variable noise and activities levels from neighboring traffic and businesses
	Storage	Storage conditions reflect room temperature (20-25 °C, 68-77 °F), with excursions allowable up to 15-30 °C, (59-86 °F), and standard home conditions	Usability lab set up to represent a home bathroom environment. Lab set at room temperature. Countertop/tabletop surfaces will be provided.
	Conditions of Visibility	Lighting varies from adequate to darkened, standard for a home setting	The usability lab will include overhead LED lighting
	Physical	Standard ambient conditions (temperature, relative humidity) apply	Usability lab set to room temperature (68-77°F) with standard relative humidity
	Mobility	The product is intended to be a handheld applicator used at rest	Participants will be able to stand or be seated
Sequence of Study		• Task 1: Simulated use scenario • Subjective data collection and root cause analysis • Task 2: Comprehension questions • Subjective data collection and root cause analysis	

3 RESULTS AND ANALYSES

Table 3 describes the study results, [Botanix SB, Inc.](#)'s analyses of the results, and DMEPA 1's analyses and recommendations.

APPEARS THIS WAY ON ORIGINAL

Table 3: HF Validation Study Results									
Legend: UE = use error; CC = close call; UD = use difficulty; URR = use-related risk analysis; RCA = root cause analysis Participants ID: P#=pediatric patient participant; A#=adult patient participant; C#=caregiver Scenario Type: Results from Both Scenarios of Unaided Rescue #1 and #2 and Knowledge Task Assessment are combined in the table below									
Information Supplied by Applicant	DMEPA's Areas of Dissent and Recommendations								
<u>Task:</u> Check Expiration Date <table border="1"> <tr> <td>Errors:</td><td>Participant Type:</td></tr> <tr> <td>UE (n=25)</td><td>12 pediatric patients; 6 adult patients; 7 adult caregivers</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=25)	12 pediatric patients; 6 adult patients; 7 adult caregivers	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=25)	12 pediatric patients; 6 adult patients; 7 adult caregivers								
CC (n=0)									
UD (n=0)									
Observed error(s): 25 participants did not check the expiration date during simulated use									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use errors is underdose.									
Relevant RCA/Subjective Feedback/Observation: Participants reported that they do not typically check the expiration dates on this type of product in general, and/or that they do not check the expiration dates on new products that they have just picked up from the pharmacy. Based on the participants' feedback, the root cause is attributed to negative transfer.									
Applicant Comment and Proposed Mitigations: - Efficacy of the drug is greater at expiration date 15%, but efficacy has still been clinically observed from the 5% sofipirionium bromide strength in the following contexts: - ECCLOCK®, which is a commercially available product on the market in Japan, at 5% sofipirionium bromide content - Phase 2 safety and efficacy study of 5%, 10%, and 15% gel (BBI-4000-CL-203). - The proposed product shelf life is 3 years. - Standard pharmaceutical practice for the pharmacist is to verify the expiration date before product is dispensed to the patient.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								

- This risk is not unique to this product. Checking expiration date is commonly expected for combination products and the risk mitigations have been focused on ensuring that the expiration date format follows FDA guidance. - The expiration date has been shown to be legible and comprehensible on the product labeling. When referring to the instructions, participants were able to comprehend the information for this step. - This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
<u>Task: Wipe Underarms</u> <table border="1" data-bbox="348 605 747 782"> <tr> <th>Errors:</th><th>Participant Type:</th></tr> <tr> <td>UE (n=23)</td><td>12 pediatric patients; 8 adult patients; 3 caregivers</td></tr> <tr> <td>CC (n=1)</td><td>1 caregiver</td></tr> <tr> <td>UD (n=1)</td><td>1 caregiver</td></tr> </table>	Errors:	Participant Type:	UE (n=23)	12 pediatric patients; 8 adult patients; 3 caregivers	CC (n=1)	1 caregiver	UD (n=1)	1 caregiver	
Errors:	Participant Type:								
UE (n=23)	12 pediatric patients; 8 adult patients; 3 caregivers								
CC (n=1)	1 caregiver								
UD (n=1)	1 caregiver								
Observed use issue(s): - Use Errors: 23 participants did not wipe underarms - Close Call: 1 participant initially wiped the manikin's right underarm but not the left underarm but realized this before applying the gel to the left underarm. - Use Difficulty: 1 participant dried the manikin's underarms but tried to dry the underarms over the manikin's t-shirt.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include an underdose.									
Relevant RCA/Subjective Feedback/Observation: - P3 did not perform this step and said that normal deodorant does not require preparing underarms. P3 had not seen the step in the instructions before but said the information in Step 7 was clear. The Applicant attributed the root cause to negative transfer. - P7, P8, and P15 did not look at the instructions and did not perform this step. P8 thought interacting with the product would be self-explanatory based on her experience with other prescription products and would also like to talk to a doctor about how to use it if that was an option for this type of product.									

P15 stated customers are typically just ready to open the box and use the product without referring to the instructions and described how other “deodorants” can be applied directly to the underarms. When prompted to look at the instructions and attempt an additional use of the product, the participants did not complete this step. P7 stated it was like a deodorant. The Applicant attributed the root cause to negative transfer of not needing to refer to the IFU of similar products.

- A1 reported that he had seen this step in the instructions but did not understand the importance. A1 stated the information is clear but should be reiterated in the instructions. The Applicant attributed the root cause to oversight of the information in the instructions.
- A14 said she independently realized when she was applying the gel that she had skipped a step. A14 said there were too many instructions and she “got lost” following through the steps. The Applicant attributed the root cause to oversight of the information in the instructions.
- P6, P11, A7, and A8 had seen in the instructions to dry underarms but reported that they felt their underarms were already dry, so they did not need to perform the task. P11 also stated that there were a lot of preparation steps for this product, so she skipped forward to the instructional steps on how to apply the product. The Applicant attributed the root cause to user mental model of not needing to dry their underarms if they were already dry.
- A13 performed first use of the product without looking at the instructions and skipped this step. Without moderator prompting during the simulated use scenario, the participant then identified and read the instructions, commenting “Oh, I did this wrong” and performed an additional use of the product. A13 did not dry his underarms. The participant said he understood the instructions but did not dry his underarms because he felt they were already dry. The Applicant attributed the first use root cause to overlooking the IFU, and the second root cause to user mental model of not needing to dry their underarms if they are already dry.
- C1 realized on their own (during debrief) that she forgot to dry the manikin’s underarms. She had noticed the information in the instructions but had forgotten the step because the manikin was not real. C1 said with her own child she would be more conscious of ensuring underarms were clean and dry. The Applicant

attributed the root cause to study artifact. • C13 and C15 said that they had seen this information in the instructions, but because they were applying the product to a manikin, they did not think they needed to dry the underarms. The Applicant attributed the root cause to study artifact. • P1 (during debrief) reported that he saw this step in the instructions but did not see the provided towel within the provided study setup. The Applicant attributed the root cause to study artifact. • P9 and A11 both skipped drying their underarms. These participants moved between the study table and the sink at Step 6. P9 said she skipped this step because she moved from the sink to the table between performing Step 6 and Step 8. A11 said she skipped the information on drying the underarms because she was already in the process of preparing the applicator, so she continued directly to the information in Step 7: (b) (4) on preparing the applicator and skipped the information in Step 7 on preparing the skin. Both reported the information to be clear. The Applicant attributed the root cause for both to study artifact. • P2, P5, and P14 saw the information in the instructions and thought it was clear, and there was no reason why they did not complete this task. Close Call: • C4 said he was trying to follow the instructions and looking at the instructions is what made him realize he had forgotten to wipe the second underarm. The Applicant attributed the root cause to oversight of the information. Use Difficulty: • C5 understood the arms should be dry. Per the moderator, it appeared that C5 was nervous and embarrassed that she performed this task over the shirt. The Applicant attributed the root cause to study artifact.	
Applicant Comment and Proposed Mitigations: • Efficacy of the drug is greater at expiration date 15%, but efficacy has still been clinically observed from the 5% sofipirionium bromide strength in the following contexts: - o ECCLOCK®, which is a commercially available product on the market in Japan, at 5% sofipirionium bromide content - o Phase 2 safety and efficacy study of 5%, 10%, and 15%	We note that the use errors related to this task may result in underdose. Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall information density that contributed to some of these use errors. Thus, additional mitigations could be implemented. See section 4.1.

gel (BBI-4000-CL-203). • If there is underarm wetness, absorption of the gel may be reduced. We maintain that absorption impact is minimal or none if underarms are not wet (as six of the participants reported). • The product workflow is aligned with other underarm products on the market. Drysol is a commercially available antiperspirant that also instructs the user to dry the skin completely prior to application. • The IFU describes (b) (4) • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. • Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. • As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
Task: Remove Cap from Applicator <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=3)</td><td>3 pediatric patients</td></tr> <tr> <td>CC (n=1)</td><td>1 adult patient</td></tr> <tr> <td>UD (n=2)</td><td>2 pediatric patients</td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=3)	3 pediatric patients	CC (n=1)	1 adult patient	UD (n=2)	2 pediatric patients	
Errors:	Participant Type:								
UE (n=3)	3 pediatric patients								
CC (n=1)	1 adult patient								
UD (n=2)	2 pediatric patients								
Observed use issue(s): • Use Errors: P7, P8, and P15 did not initially read the instructions and did not remove the cap. • Close Call: A13 did not initially read the instructions and did not remove the cap; however, without moderator prompting during the simulated use scenario, the participant then identified and read the instructions, commenting "oh I did this wrong" and performed an additional use of the product.									

Use Difficulties: P6 and P10 experienced difficulty removing the cap. Both participants initially attempted to twist to remove the cap, then were able to remove the cap successfully.	
Risk associated with Task Errors (Per Applicant URRR): The potential harm associated with these use issues include inconvenience to patient and delayed/untreated hyperhidrosis.	
Relevant RCA/Subjective Feedback/Observation: Use Errors: - P7 stated that he thought the product was like a deodorant and reported that it was strange to have things stacked together (pump, applicator, cap), but figured out there were multiple pieces to the product through trial and error. P8 reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor on the use of the product if that was an option for the product. P15 stated customers are typically just ready to open the box and use the product without referring to the instructions. When prompted to look at the instructions and perform an additional use of the product, the participants removed the cap. The Applicant attributed the root cause to negative transfer. Close Calls: - On the second attempt the participant removed the cap. A13 described that he learned to remove the cap through the diagram on Step 1. The Applicant attributed the root cause to oversight of the IFU. Use Difficulties: - P6 stated she tried to twist the cap because of her “instinct” like how she twists off caps on soda bottles. P6 reported that the instructions helped her figure out how to pull the cap, it was easy to remove. P10 said that once he looked at Step 5 in the instructions, he had seen how to remove the cap correctly. The Applicant attributed the root cause to negative transfer.	
Applicant Comment and Proposed Mitigations: - There are no critical risks associated with not removing the cap from the applicator. When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events. - The carton and bottle labeling emphasize the importance of	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.

thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added (1) on the top flap of the carton, (2) on the primary panel of the carton, and (3) on the front bottle label. The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) (b) (4)									
Task: Press the Pump Down over the Sink (i.e., priming) <table border="1" data-bbox="348 483 747 662"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=10)</td><td>7 pediatric patients; 1 adult patient; 2 caregivers</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=10)	7 pediatric patients; 1 adult patient; 2 caregivers	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=10)	7 pediatric patients; 1 adult patient; 2 caregivers								
CC (n=0)									
UD (n=0)									
Observed use issue(s): 10 participants did not completely depress the pump into the sink until the gel comes out (i.e., does not prime).									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include an underdose or an overdose.									
Relevant RCA/Subjective Feedback/Observation: - P3 did not prime the pump and reported that she had seen Step 6 in the instructions previously; however, the participant reported that she had skimmed through the instructions since she thought she already understood how to use the product based on what she "typically does" for products like this. She stated the information was clear. The Applicant attributed the root cause to negative transfer. - P6 said that she did not prime the pump because she expected the gel to come out of the pump easily from prior experience. The moderator prompted her to perform the task in Step 6, and the participant performed the task correctly. The Applicant attributed the root cause to negative transfer. - P7, P8, and P15 did not prime the pump and did not read the instructions before use of the product. P7 thought the product was like a deodorant. P8 thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also stated she would talk to the doctor if that was an option for this product. P15 stated	We disagree with the Applicant's determination of the root cause for P1's use issue. Based on the information provided, it also appears that the IFU format/layout was also a root cause of the use issue; that is, the folding of the IFU led the user to not see all of the instructions.								

customers are typically just ready to open the box and use the product without referring to the instructions and described how other “deodorants” can be applied directly to the underarms. The moderator prompted the participants to look at the instructions and perform an additional use of the product. On the second use, the participants primed the pump. The Applicant attributed the root cause to negative transfer. • C15 did not read the instructions before use of the product and skipped this step. C15 stated they would have read the IFU if he were applying the gel “to a real human being” and “would want to make sure he had done it correctly.” The moderator prompted him to look at the instructions and perform a second use of the product, during which C15 did not prime the pump. He stated that he was unsure why he couldn’t apply the gel directly to the applicator because in his experience with similar products, the pump would not require priming, and the drug came out of the pump right away. The Applicant attributed the initial use error to study artifact, and the second use error to negative transfer. • P1 did not prime the pump and said he was focused on Step 8 for learning how to apply the gel to the applicator. P1 state that he understood Step 6 but said he had not seen the step in the instructions. When P1 was looking at the instructions during simulated use, he had the instructions folded so that Step 6 was facing away from him. The Applicant attributed the root cause to information oversight. • C4 referred to the instructions during simulated use but skipped this step. C4 (during debrief) independently decided to look over the IFU, and then noticed Step 6, at which point they realized that he forgot to prime the pump. C4 stated the information was clear. C4 also stated that the information in the step was highlighted in red but suggested to highlight the step number (6). C4 said he was more focused on preparing the patient then he was on preparing the medicine/pump. The Applicant attributed the root case to oversight of information. • P14 referred to the instructions during simulated use but skipped this step. P14 stated the information was clear in this step. They said they were focused on the images in the instructions and had not previously noticed the text information in Step 6. The Applicant attributed the root cause to oversight of the information. • A13 did not read the instructions before use of the product and	
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skipped this step. Without moderator prompting during the simulated use scenario, A13 then identified and read the instructions, commenting "Oh, I did this wrong" and performed an additional use of the product, during which A13 also did not prime the pump. A13 reported that he interpreted the information in Step 6 to mean that he should apply the product over a sink. The Applicant attributed the root cause to oversight of IFU and information of the IFU.	
Applicant Comment and Proposed Mitigations: • Efficacy of the drug is greater at expiration date 15%, but efficacy has still been clinically observed from the 5% sofipironium bromide strength in the following contexts: ○ ECCLOCK®, which is a commercially available product on the market in Japan, at 5% sofipironium bromide content. ○ Phase 2 safety and efficacy study of 5%, 10%, and 15% gel (BBI-4000-CL-203). • For overdose BBI has conducted two clinical studies that demonstrate that a one-time dose 6-fold above the therapeutic dose did not cause a meaningful increase in any adverse events (BBI-4000-CL-106: QT prolongation study, BBI-4000-CL-109: pharmacokinetics and dose safety study). None of the participants in the HF Validation Study applied more than 6 pumps to their body across all tasks. • The use related issues for failure to prime or priming incorrectly may be a first use only issue because priming is only required for first use. Therefore, these use-related issues are not expected to occur repeatedly during the course of using the product. • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added (1) on the top flap of the carton, (2) on the primary panel of the carton, and (3) on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • When referring to the instructions, participants were able to comprehend the information for this step. • This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall information density that contributed to some of these use errors. Thus, additional mitigations could be implemented. See section 4.1.

needed to further address the use-related events.										
Task: Deposit Gel onto the Applicator <table><tr><td>Errors:</td><td>Participant Type:</td></tr><tr><td>UE (n=15)</td><td>8 pediatric patients; 4 adult patients; 3 caregivers</td></tr><tr><td>CC (n=1)</td><td>1 adult patient</td></tr><tr><td>UD (n=1)</td><td>1 adult patient</td></tr></table>		Errors:	Participant Type:	UE (n=15)	8 pediatric patients; 4 adult patients; 3 caregivers	CC (n=1)	1 adult patient	UD (n=1)	1 adult patient	
Errors:	Participant Type:									
UE (n=15)	8 pediatric patients; 4 adult patients; 3 caregivers									
CC (n=1)	1 adult patient									
UD (n=1)	1 adult patient									
Observed use issue(s): - Use Errors: 15 participants did not apply the gel onto the applicator or applied more than 1 pump. - Close Call: 1 participant initially pumped gel into a paper towel and applied it to the underarm. - Use Difficulty: 1 participant initially asked the moderator for an applicator, such as cotton rounds. The participant then picked up the applicator and noted that she would be able to apply the gel with the applicator.										
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Another potential harm associated with these use issues include an underdose or an overdose.										
Relevant RCA/Subjective Feedback/Observation: - P7 did not refer to the instructions and applied the gel to his hands instead of the applicator. P7 said he initially applied the gel to his hands because he did not know what the applicator was until he had looked at the instructions in Step 8. The moderator prompted P7 to reference the instructions and perform a second use of the product, and on the second use P7 applied 1 pump of gel to the applicator. P7 stated that the product was like a deodorant. The Applicant attributed the root cause to negative transfer. - P8 did not read the instructions and applied more than one pump of gel directly to the underarm instead of the applicator. She reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She stated she would talk to the doctor on how to use it if that was an option for this type of product. The participant was then prompted to perform another use of the product using										

the instructions and applied 2 pumps of gel to the applicator, stating that when she applied the gel, the pump did not “go down all the way” so she applied a second pump. The Applicant attributed the root cause to negative transfer and incompletely depressing the pump. • P15 did not read the instructions and applied the gel directly to the underarms instead of the applicator. P15 stated customers are typically just ready to open the box and use the product without referring to the instructions and described how other “deodorants” can be applied directly to the underarms. When prompted to review the instructions and perform a second use of the product, during which the participant applied the gel to the applicator. The Applicant attributed the root cause to negative transfer. • P1 and A1 applied multiple pumps of gel to the applicator. Both participants used the instructions during simulated use. P1 and A1 reported they thought they could apply the pumps of gel for both underarms to the applicator at the same time. When prompted to look at Step 8 and Step 9 in the instructions, they understood that the gel should be reapplied between underarms. The Applicant attributed the root cause to oversight of information. • P5 applied multiple pumps of gel. P5 thought that the instructions had said to “pump until the top surface is covered.” The participant reread the instructions and saw to apply 1 pump of gel. P5 stated she was focused on covering the surface of the applicator, but after reviewing the instructions understood the information. The Applicant attributed the root cause to oversight of information. • C10 and P14 applied more than 1 pump of gel. The participants commented that they based the amount of gel to apply on the images in step 8. P14 said he was confused on the images in the IFU and had not previously noticed the information in Step 6. When looking at the instructions again, the participants understood to apply 1 full pump of gel. The Applicant attributed the root cause to oversight of the information. • P3 applied more than 1 pump of gel and described that she wanted to apply enough gel to cover the top surface of the applicator. She opened the IFU but did not reference them often during simulated use. When referring to the IFU, she understood to apply 1 pump per underarm. The Applicant attributed the root	
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cause to mental model.

- A12 applied more than 1 pump of gel and said she applied gel until applicator top was full. Later during simulated use, she saw in the instructions Step 8 that she should have applied 1 full pump of gel. The Applicant attributed the root cause to mental model.
- P6 initially applied less than 1 full pump of gel because she skipped the priming step, and instead deposited gel directly on applicator. She then added an additional full pump of gel. She stated she had seen in the IFU to apply 1 pump of gel, but she did not think she had enough gel to cover the entire underarm area, so she added additional gel. The Applicant attributed the root cause to mental model.
- C4 knew from the IFU to apply 1 pump of gel but applied additional gel because a small amount of gel slid down the side of the applicator. C4 held the applicator so that the flat surface was vertical. C4 thought that the pump needed to be kept upright, so he tilted the applicator to apply the gel. The Applicant attributed the root cause to mental model.
- A6 applied multiple pumps of gel because she reported that she was unsure of how much gel to apply. When referring to the IFU, she understood to apply 1 full pump of gel. She stated she did not see this information previously because there was too much information in the instructions, and it was overwhelming. The Applicant attributed the root cause to density of information.
- A5 applied more than 1 pump of gel. A5 said she was focused on how to apply the product to her underarm, not on how much product should be dispensed on the applicator. The Applicant attributed the root cause to being focused on the application technique instead of dosing.
- C15 did not read the IFU and applied the gel to his hands before applying to the manikin's underarms. C15 commented that he would have read the IFU if he were applying the gel "to a real human being" and "would want to make sure he had done it correctly." C15 was prompted to review the instructions and perform a second attempt. On the second attempt, C15 applied 1 pump of gel to the applicator. The Applicant attributed the root cause to study artifact.

Close Call:

- A13 performed first use of the product without look at the IFU. Without moderator prompting during the simulated use scenario,

A13 then identified and read the instructions, commenting “Oh, I did this wrong” and performed an additional use of the product. On the first attempt, the participant deposited the gel onto a paper towel and then the underarm. On the second attempt, the participant applied gel to the applicator. A13 noted that Step 5 in the IFU informed him to apply gel to the applicator. The Applicant attributed the root cause to oversight of the IFU. Use Difficulty: A4 asked the moderator for an applicator, such as cotton rounds. A4 then picked up the applicator and noted that she would be able to apply the gel with the applicator. A4 said that she would typically use her own organic cotton rounds because she did not like using plastics. The Applicant attributed the root cause to judgment to avoid skin contact with plastic.	
Applicant Comment and Proposed Mitigations: - The exposure risk associated with using their hands to apply the gel is mitigated if the participants washed their hands. C15 did wash their hands. - For underdose, the efficacy of the drug is greater at 15%, but efficacy has still been clinically observed from the 5% sofipirionium bromide strength in the following contexts: - ECCLOCK[®], which is a commercially available product on the market in Japan, at 5% sofipirionium bromide content - Phase 2 safety and efficacy study of 5%, 10%, and 15% gel (BBI-4000-CL-203). - For overdose, BBI has conducted two clinical studies that demonstrate that a one-time dose 6-fold above the therapeutic dose did not cause a meaningful increase in any adverse events (BBI-4000-CL-106: QT prolongation study, BBI- 4000-CL-109: pharmacokinetics and dose safety study). Throughout any of the use scenarios. None of the participants in the HF validation study applied more than 6 pumps of gel to their body. - Blurred vision, mydriasis, dry mouth, and urinary hesitation require systemic exposure following topical application to the skin and are more likely to be observed following a dose of at least 2 pumps to a larger surface area. Only one study participant applied gel to their hands instead of their underarms (P7), which is unlikely to elicit the harms associated with this error, due to poor absorption through the skin of the hands. The risk exposure of the product to the eyes or mouth did not occur for any	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall information density that contributed to these use errors. Additionally, we find that users were unable to identify what the applicator was, how to use it, or applied more than one pump to their skin. These use errors can contribute to the risk of overdose or inadvertent exposure of others, including symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Some participants also attributed use errors to information density of/overlooking information in the IFU. Therefore, we identified additional mitigations that could be implemented to reduce this risk. See section 4.1.

participants. • The pump has been designed to dispense a uniform, fixed amount of the drug in order to help users achieve the correct dose for each use. This design feature minimizes reliance on the user to determine how much gel should be applied to each underarm, which is clearly illustrated and described within the IFU. Users applied judgment to move beyond the content laid out in the IFU for how much gel should be dispensed onto the applicator, which is acceptable given the margins for safety and efficacy as described above for under and overdosing. The user interface has been optimized to the extent possible and practical and accept the residual risks. • The applicator is designed to allow for easy application to the underarm without significant edges that would make application more challenging. The applicator does include a small ridge around its circumference to help gel stay on top, which minimizes drips and helps drive consistency in the gel volume that is delivered to the underarm. • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading “STOP!” with a red stop sign graphic and text underneath “You MUST read the instructions” was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • The instructions clearly state to (b) (4) and apply “one full pump” pf gel to the applicator. When referring to the instructions, participants were able to comprehend the information for this step. • This demonstrates the effectiveness of the instructions. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
Task: Use Applicator to Apply Gel to Underarm <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=5)</td><td>4 pediatric patients; 1 caregiver</td></tr> <tr> <td>CC (n=1)</td><td>1 adult patient</td></tr> <tr> <td>UD (n=1)</td><td>1 caregiver</td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=5)	4 pediatric patients; 1 caregiver	CC (n=1)	1 adult patient	UD (n=1)	1 caregiver	
Errors:	Participant Type:								
UE (n=5)	4 pediatric patients; 1 caregiver								
CC (n=1)	1 adult patient								
UD (n=1)	1 caregiver								

Observed use issue(s): • Use Errors: 5 participants did not use the applicator to apply gel to underarm • Close Call: 1 participant initially did not attempt to apply gel with applicator. • Use Difficulty: 1 participant applied the gel to the manikin's underarms.	
Risk associated with Task Errors (Per Applicant URR): • The potential harm associated with these use issues include exposure risk which could lead to local site reaction, transient mydriasis, blurred vision, dry mouth, and urinary hesitation.	
Relevant RCA/Subjective Feedback/Observation: Use Errors: • P7 did not refer to the IFU and applied the gel to his hands instead of the applicator or his underarms. P7 said he initially applied the gel to his hands because he did not know what the applicator was until he had looked at the instructions in Step 8. The moderator prompted P7 to reference the instructions and perform a second use of the product, and on the second use P7 used the applicator to apply the product to the underarms. P7 stated that the product was like a deodorant. The Applicant attributed the root cause to negative transfer. • P8 and P15 did not read the instructions and pumped the gel directly onto the armpits without using the applicator. P8 reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor about how to use it if that was an option for this type of product. P15 commented that customers are typically just ready to open the box and use the product without referring to the instructions and described how other "deodorants" can be applied directly to the underarms. The moderator prompted the participants to reference the IFU and perform a second use of the product. On second use of the product, the participants used the applicator to apply the gel to their underarms. The Applicant attributed the root cause to negative transfer. • P4 applied the gel using the applicator but tilted the applicator and spilled some gel on his hand. P4 reported that the skin barrier was bent so he had to tilt the applicator in order to apply the gel onto the skin barrier. The Applicant attributed the root cause to study artifact.	We disagree with the Applicant's root cause determination for P4's use issue. Users of this product may have to tilt the applicator to apply to the underarm(s); therefore, although in this case the root cause may be related to the placement of the manikin, this is a foreseeable use issue for this product.

- C15 did not read the IFU before use of the product and applied the gel to the manikin's underarms using his hands instead of the applicator. The participant commented that he would have read the IFU if he were applying the gel "to a real human being" and "would want to make sure he had done it correctly." The moderator then prompted the participant to look at the IFU and perform a second use of the product, during which the participant used the applicator to apply the gel. The Applicant attributed the root cause to study artifact. Close Call: - A13 first used the product without looking at the IFU. On the first attempt, the participant applied the gel using a paper towel. Without moderator prompting during the simulated use scenario, the participant then identified and read the IFU, commenting "Oh, I did this wrong" and performed an additional use of the product. On the second attempt, the participant applied the gel using the applicator. A13 noted that Step 5 (b) (4) in the IFU informed him to apply the gel to the applicator. The Applicant attributed the root cause to oversight of the IFU. Use Difficulty: - C5 applied the gel to the manikin's underarms over the manikin's shirt. The participant said if it was a real person, she would have applied the gel directly to the underarms. The participant understood that the gel should be applied to the underarms. Based on the moderator observation, the participant was nervous and embarrassed that she performed the task over the shirt. C5 understood that the product should be applied to the underarms. The Applicant attributed the root cause to study artifact.	
Applicant Comment and Proposed Mitigations: - Pediatric patients may work with a caregiver for the first use, or have a caregiving supervising first use, which would be a further mitigation for the pediatric participants, who were responsible for most of the incorrect application location use events. - Although they did not use the correct application technique, some participants applied the gel directly onto the skin pad in the armpits successfully. As no gel spilled during this step, there is no risk of exposure for these participants. - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that users were unable to identify what the applicator was, how to use it, or applied more than one pump to their skin. These use errors can contribute to the risk of overdose or inadvertent exposure of others, including symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. We identified additional mitigations that could be implemented to reduce this risk. See section 4.1.

and text underneath “You MUST read the instructions” was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
Task: Transfer Applicator and Pump to Opposite Hands [If self-administering] <table border="1" data-bbox="348 605 747 753"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=2)</td><td>1 pediatric patient; 1 adult patient</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=2)	1 pediatric patient; 1 adult patient	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=2)	1 pediatric patient; 1 adult patient								
CC (n=0)									
UD (n=0)									
Observed use issue(s): 2 participants did not transfer pump to opposite hands.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include delayed access to device system leading inconvenience to patient with no clinical adverse effect, delayed or untreated hyperhidrosis and exposure to sharp edges leading to temporary discomfort.									
Relevant RCA/Subjective Feedback/Observation: - P7 did not read the instructions. P7 applied the gel to his hands and did not apply to his underarms. P7 initially applied the gel to his hand because he said he did not know what the applicator was or that it was needed until he had referenced the IFU. After the first attempt and debrief, the moderator prompted P7 to review the IFU and attempt a second use of the product. On the second use, the participant performed the task correctly. During debrief, P7 described that he thought the product was like a deodorant. The Applicant attributed the root cause to negative transfer. - A5 only applied the product to 1 underarm and did not transfer the pump to the opposite hand to apply the product for the second underarm. During debrief, the participant was asked to	We disagree that the root cause of “P7”’s use error was negative transfer, because the participant clearly stated that they were not aware what the applicator was. This participant’s use error appears to be related to the use error experienced for the task “Use Applicator to Apply Gel to Underarm”.								

apply the gel to the second underarm and completed the task successfully. A5 only described applying the product to her left underarm and was provided with 1 skin barrier for the left underarm. During debrief, the participant said that she had seen in the IFU to do the second underarm. She did not apply product to the second underarm because her left underarm is the one that experiences excessive sweating. The Applicant attributed the root cause to user judgment of where the product should be applied for her clinical condition.									
Applicant Comment and Proposed Mitigations: - There are no critical risks associated with not transferring the applicator and pump to the opposite hand. The carton and bottle labeling emphasize the importance of thoroughly referring to the IFU to help promote successful use. - Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - We have determined that no additional changes to the user interface are needed to further address the use-related events.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that users were unable to identify what the applicator was, how to use it, or applied more than one pump to their skin. These use errors can contribute to the risk of inadvertent exposure of others. We identified additional mitigations that could be implemented to reduce this risk. See section 4.1.								
Task: Deposit Gel onto Applicator for Second Underarm <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=12)</td><td>6 pediatric patients; 3 adult patients; 3 caregivers</td></tr> <tr> <td>CC (n=1)</td><td>1 adult patient</td></tr> <tr> <td>UD (n=1)</td><td>1 caregiver</td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=12)	6 pediatric patients; 3 adult patients; 3 caregivers	CC (n=1)	1 adult patient	UD (n=1)	1 caregiver	
Errors:	Participant Type:								
UE (n=12)	6 pediatric patients; 3 adult patients; 3 caregivers								
CC (n=1)	1 adult patient								
UD (n=1)	1 caregiver								
Observed use issue(s): - Use Errors: 12 participants did not apply gel onto applicator for second underarm, applied more than 1 pump, or did not apply to the applicator at all. - Close Call: 1 participant initially applied gel to paper towel before self-correcting. - Use Difficulty: 1 did not reapply the gel initially, but then paused referring to the IFU and corrected.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include									

exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Another potential harm associated with these use issues include an underdose or an overdose.	
Relevant RCA/Subjective Feedback/Observation: Use Errors: • P7 did not read the instructions. P7 applied the gel to his hands and did not apply to his underarms. P7 initially applied the gel to his hand because he said he did not know what the applicator was or that it was needed until he had referenced the IFU. The moderator prompted the participant to perform a second use of the product after referring to the instructions. On the second use, the participant did not reapply gel for the second underarm. When debriefing after the second use of the product, P7 described that the product was like a deodorant. P7 thought the gel could be applied to both underarms without additional steps in between underarm applications. The Applicant attributed the root cause to negative transfer. • P8 did not read the IFU and applied more than 1 pump of gel directly to the underarm (not to the applicator). P8 reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor about how to use it if that was an option for this type of product. During debrief, the participant was prompted to reference the instructions and perform a second attempt. On the second attempt, the participant correctly applied 1 pump of gel to the applicator. The Applicant attributed the root cause to negative transfer. • P15 did not read the IFU and applied the gel directly onto the armpits without using the applicator. P15 commented that customers are typically just ready to open the box and use the product without referring to the IFU and described how other “deodorants” can be applied directly to the underarms. When prompted to review the IFU and perform a second use, the participant did not reapply gel to the applicator between underarms. P15 understood from looking at the instructions Step 8: (b) (4) and Step 9 (b) (4) to apply a second pump of gel to the second underarm. The participant said the information was clear, but he had not seen the information in the IFU during the simulated use. The Applicant attributed the	

root cause to negative transfer.

- P1 and A1 did not apply additional gel for the second underarm. The participants referred to the IFU and applied 2 pumps of gel before the first underarm application. P1 reported that he initially thought from looking at the IFU that the gel for both underarms could be applied to the applicator at the same time. A1 commented that he tried to spread an even amount of gel under each underarm. After reviewing Step 8 (b) (4) in the IFU, the participants understood that gel should be reapplied to the applicator between underarms. The Applicant attributed the root cause to oversight of information in IFU.
- P14 did not apply additional gel for the second underarm. The participant said he did not read the IFU closely and was instead focused on the images. P14 understood from looking at the instructions Step 9: (b) (4) to apply a second pump of gel to the applicator. The Applicant attributed the root cause to oversight of text in the IFU.
- C4 applied more than 1 pump of gel for the second underarm. C4 knew from the instructions to apply only 1 pump of gel but applied additional gel because some of the gel slid down the side of the applicator. C4 held the applicator so that the flat surface was vertical. The participant thought that the pump needed to be kept upright, so he tilted the applicator to apply the gel. After reviewing the IFU, C4 understood that users can tilt the pump and the applicator should be kept upright. The Applicant attributed the root cause to misinterpreting information in the IFU.
- A5 initially only applied the product to 1 underarm and did not deposit gel on the applicator for the second side. The participant explained that her left underarm experienced excessive sweating. After the simulated use tasks, the moderator prompted her to apply the gel to the other underarm as well to ensure all critical tasks were evaluated. During this task, A5 applied more than 1 pump of gel. The participant said she was focused on how to apply the product to her underarm, not on how much product should be dispensed on the applicator. The Applicant attributed the root cause of the first use issue to user judgment of where the product should be applied for her clinical condition. The Applicant attributed the root cause of the second use issue to being focused on application technique and not focused on dosing.

- A6 applied more than 1 pump of gel for the second underarm application. A6 was unsure how much gel to apply. The participant said she did not see this information during simulated use because there was too much information in the instructions, and it was overwhelming. A6 understood from the IFU that you should apply 1 full pump of gel. The Applicant attributed the root cause to density of information.
 - P2 did not apply additional gel for the second underarm. P2 reported that he thought it was okay to apply 1 pump of gel to the applicator and apply to both underarms. The participant said he had not initially seen the information about the additional gel in the IFU, but that this information was clear. Based on moderator observation, the participant was following the IFU step-by-step and had applied a pump of gel to the applicator when he was stopped and asked to put on the skin barriers. This interruption may have caused him to miss a step in the instructions. The Applicant attributed the root cause to study artifact.
 - C10 did not apply additional gel for the second underarm. C10 said there was still gel left on the applicator after the first underarm, so he applied directly to the second underarm. The instructions did not say to clean the applicator between underarms, so the participant assumed he could apply remaining product directly to the second underarm. Based on expert analysis, gel may have remained on the applicator because the surface of the manikin's underarm is a hard plastic, allowing for minimal absorption of the gel. This lack of absorbent material makes it probable that some gel remains on the surface of the applicator. The Applicant attributed the root cause to study artifact.
 - C15 did not read the instructions and applied the gel to his hands, before applying to the manikin's underarm. C15 stated he would have read the IFU if he were applying the gel "to a real human being" and "would want to make sure he had done it correctly." After debriefing, the participant was prompted to review the instructions and perform a second attempt. On the second attempt, the participant applied 1 pump of gel to the applicator. The Applicant attributed the root cause to study artifact.
- Close Call:
- A13 first used the product without looking at the instructions. On the first attempt, the participant applied the gel using a paper

towel. Without moderator prompting during the simulated use scenario, the participant then identified and read the IFU, commenting “Oh, I did this wrong” and performed an additional use of the product. On the second attempt, the participant applied the gel using the applicator. A13 noted that Step 5. (b) (4) in the IFU informed him to apply the gel to the applicator. The Applicant attributed the root cause to oversight of the IFU. Use Difficulty: C9 did not reapply the gel at first, then paused referring to the IFU, and then finally correctly completed the step. A very small amount of gel spilt off the applicator. The participant wiped the gel off the side of the applicator, reportedly to avoid spreading. C9 saw to do an additional pump for the second underarm after referencing the IFU for a period of time. The participant said a small amount of gel may have spilled off the applicator because he was tilting the applicator. The participant said he felt he was still able to apply the full dose to the manikin. The Applicant attributed the root cause to oversight of the information.	
Applicant Comment and Proposed Mitigations: - The exposure risk associated with using their hands to apply the gel is mitigated if the participants washed their hands. C15 did wash their hands. - For underdose, the efficacy of the drug is greater at 15%, but efficacy has still been clinically observed from the 5% sofipirionium bromide strength in the following contexts: - ECCLOCK®, which is a commercially available product on the market in Japan, at 5% sofipirionium bromide content - Phase 2 safety and efficacy study of 5%, 10%, and 15% gel (BBI-4000-CL-203). - For overdose, BBI has conducted two clinical studies that demonstrate that a one-time dose 6-fold above the therapeutic dose did not cause a meaningful increase in any adverse events (BBI-4000-CL-106: QT prolongation study, BBI- 4000-CL-109: pharmacokinetics and dose safety study). Throughout any of the use scenarios. None of the participants in the HF validation study applied more than 6 pumps of gel to their body. - Blurred vision, mydriasis, dry mouth, and urinary hesitation require systemic exposure following topical application to the	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall information density that contributed to these use errors. Additionally, we find that users were unable to identify what the applicator was, how to use it, or applied more than one pump to their skin. These use errors can contribute to the risk of overdose or inadvertent exposure of others, including symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Thus, additional mitigations could be implemented. See section 4.1.

skin and are more likely to be observed following a dose of at least 2 pumps to a larger surface area. Only one study participant applied gel to their hands instead of their underarms (P7), which is unlikely to elicit the harms associated with this error, due to poor absorption through the skin of the hands. The risk exposure of the product to the eyes or mouth did not occur for any participants. • The pump has been designed to dispense a uniform, fixed amount of the drug in order to help users achieve the correct dose for each use. This design feature minimizes reliance on the user to determine how much gel should be applied to each underarm, which is clearly illustrated and described within the IFU. Users applied judgment to move beyond the content laid out in the IFU for how much gel should be dispensed onto the applicator, which is acceptable given the margins for safety and efficacy as described above for under and overdosing. The user interface has been optimized to the extent possible and practical and accept the residual risks. • The applicator is designed to allow for easy application to the underarm without significant edges that would make application more challenging. The applicator does include a small ridge around its circumference to help gel stay on top, which minimizes drips and helps drive consistency in the gel volume that is delivered to the underarm. • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • The instructions clearly state to (b) (4) and apply "one full pump" of gel to the applicator. When referring to the instructions, participants were able to comprehend the information for this step.	
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Task Use Applicator to Apply Gel to Second Underarm <table border="1"> <tr> <th>Errors:</th><th>Participant Type:</th></tr> <tr> <td>UE (n=5)</td><td>3 pediatric patients; 1 adult patient; 1 caregiver</td></tr> <tr> <td>CC (n=1)</td><td>1 adult participant</td></tr> <tr> <td>UD (n=1)</td><td>1 caregiver</td></tr> </table>	Errors:	Participant Type:	UE (n=5)	3 pediatric patients; 1 adult patient; 1 caregiver	CC (n=1)	1 adult participant	UD (n=1)	1 caregiver	
Errors:	Participant Type:								
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CC (n=1)	1 adult participant								
UD (n=1)	1 caregiver								
Observed use issue(s): - Use Errors: 5 participants did not apply gel to the second underarm or did not use the applicator. - Close Call: 1 participant did not initially use the applicator. - Use Difficulty: 1 participant applied to the manikin's underarms over the shirt.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation.									
Relevant RCA/Subjective Feedback/Observation: Use Errors: - P7 did not read the instructions. P7 applied the gel to his hands and did not apply to his underarms. P7 initially applied the gel to his hand because he said he did not know what the applicator was or that it was needed until he had referenced the IFU. The moderator prompted the participant to perform a second use of the product after referring to the instructions. On the second use, the participant did not reapply gel for the second underarm. When debriefing after the second use of the product, P7 described that the product was like a deodorant. P7 thought the gel could be applied to both underarms without additional steps in between underarm applications. The Applicant attributed the root cause to negative transfer. - P8 did not read the IFU and applied more than 1 pump of gel directly to the underarm. P8 reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor about how to use it if that was an option for this type of product. During debrief, the participant was prompted to reference the instructions and perform a second attempt. On the second attempt, the participant correctly used the applicator to apply the gel to the									

second underarm. The Applicant attributed the root cause to negative transfer. - A5 initially only applied the product to 1 underarm and did not apply gel to the second underarm. During debrief, the moderator prompted the participant to apply gel to her second underarm to evaluate all critical tasks, and the participant performed the task correctly. A5 explained that she only applied the gel to one underarm because her left underarm experienced excessive sweating. The Applicant attributed the root cause to user judgment of where the product should be applied for her clinical condition. - C15 did not read the instructions and applied the gel to his hands, before applying to the manikin's underarm. The participant commented that he would have read the IFU if he were applying the gel "to a real human being" and "would want to make sure he had done it correctly." On the second attempt, the participant applied 1 pump of gel to the applicator. The Applicant attributed the root cause to study artifact. Close Call: - A13 first used the product without looking at the IFU. On the first attempt, the participant applied the gel using a paper towel. Without moderator prompting during the simulated use scenario, the participant then identified and read the IFU, commenting "Oh, I did this wrong" and performed an additional use of the product. On the second attempt, the participant applied the gel using the applicator. A13 noted that Step 5. (b) (4) in the IFU informed him to apply the gel to the applicator. The Applicant attributed the root cause to oversight of the IFU. Use Difficulty: - C5 applied the gel to the manikin's underarms over the manikin's shirt. C5 said if it was a real person, she would have applied the gel directly to the underarms. The participant understood that the gel should be applied to the underarms. Based on the moderator observation, the participant was nervous and embarrassed that she performed the task over the shirt. C5 understood that the product should be applied to the underarms. The Applicant attributed the root cause to study artifact.	
Applicant Comment and Proposed Mitigations: The high-risk scenario was evaluated where participants were not told the application location or indication for use. This risk is	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall

anticipated to be mitigated by the interactions patients will have with the physician and pharmacist prior to use of the product, where HCPs are likely to review the indications for use and correct application location for the product. • Additionally, pediatric patients may work with a caregiver for the first use, or have a caregiver supervising first use, which would be a further mitigation for the pediatric participants, who were responsible for most of the incorrect application location use events. • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.	information density that contributed to these use errors. Additionally, we find that users were unable to identify what the applicator was, how to use it, or applied more than one pump to their skin. These use errors can contribute to the risk of overdose or inadvertent exposure of others, including symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Thus, additional mitigations could be implemented. See section 4.1.								
Task: Rinse Applicator <table border="1" data-bbox="348 927 747 1075"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=9)</td><td>6 pediatric patients; 3 caregivers</td></tr> <tr> <td>CC (n=1)</td><td>1 adult patient</td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=9)	6 pediatric patients; 3 caregivers	CC (n=1)	1 adult patient	UD (n=0)		
Errors:	Participant Type:								
UE (n=9)	6 pediatric patients; 3 caregivers								
CC (n=1)	1 adult patient								
UD (n=0)									
Observed use issue(s): • Use Errors: 9 participants did not rinse the applicator. • Close Call: 1 participant initially did not rinse the applicator.									
Risk associated with Task Errors (Per Applicant URR): • The potential harm associated with these use issues include exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation.									
Relevant RCA/Subjective Feedback/Observation: • P7, P8, and P15 did not read the instructions and did not rinse the applicator. During debrief, P7 commented that he thought the product was like a deodorant. P8 reported that she thought									

interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor about how to use it if that was an option for this type of product. P15 commented that customers are typically just ready to open the box and use the product without referring to the instructions. The moderator prompted the participants to perform a second use of the product after referring to the instructions. On the second use, the participants rinsed the applicator. The Applicant attributed the root cause to negative transfer.

- C7 wiped the applicator with a towel but did not rinse the applicator. C7 knew from prior experience with topical products to clean the applicator. The participant saw in the instructions to wash the applicator. The participant felt that wiping the applicator off with a towel would be equivalent to rinsing the applicator, as both methods would remove the gel from the applicator. The participant said she did not rinse the applicator because she did not want water to get into the product to avoid damaging it. The Applicant attributed the root cause to mental model.
- P13 realized independently that she did not rinse off the applicator or wash her hands. The participant said she had not seen that information in the instructions because she was paying attention to the information on how to apply the product and did not read the rest of the instructions. The participant reported that the information in the instructions was clear. The Applicant attributed the root cause to mental model.
- C9 did not rinse the applicator. During debrief, the participant reviewed the instructions and acknowledged that he did not perform Step 10: (b) (4). The participant said he had skipped that information. The participant thought the steps seemed too involved and it would be helpful if there were fewer steps in the instructions. The Applicant attributed the root cause to density of information within the IFU.
- C15 did not read the instructions and did not rinse the applicator. The participant commented that he would have read the instructions if he were applying the gel "to a real human being" and "would want to make sure he had done it correctly. The participant was prompted to review the instructions and perform a second attempt. On the second attempt, the participant rinsed the applicator. The Applicant attributed the root cause to study

artifact. • P6 did not rinse the applicator. The participant had mentioned rinsing the applicator before applying the product, but then did not rinse the cap during simulated use. The participant said she had seen the information in the instructions and the information was clear. Based on moderator observation, it seemed that the participant thought the intended task for the simulated use scenario was only applying the gel and not all the tasks that would be required for a complete use of the product (including rinsing the applicator and washing hands). The Applicant attributed the root cause to study artifact of participant expectations of scope for the study session. • P1 did not rinse the applicator. P1 reviewed the instructions during debrief and saw Step 10: (b) (4) The participant said he saw and understood the information but did not think to complete the steps. It was unclear why the participant did not perform this task. Upon review, P1 reported that the information in the instructions was clear and understandable. The Applicant did not attribute a root cause to this use issue. Close Call: • A13 initially did not use the instructions and did not rinse the applicator. Without moderator prompting during the simulated use scenario, the participant then identified and read the instructions, commenting "Oh, I did this wrong" and performed an additional use of the product. On the second use, A13 rinsed the applicator. A13 said he knew from prior experience applying ointments that product remnants should not be left on the applicator, so the applicator should be cleaned. The Applicant attributed the root cause to oversight of the IFU.	
Applicant Comment and Proposed Mitigations: • Risk of exposure is mitigated if the participants replaced the cap back onto the applicator and is a mitigation for half of the participants who experienced this error; of the ten participants who experienced a use related event on this task (9 UE, 1 CC) five of them replaced the cap back onto the applicator, and five did not. • Though use events were experienced by both caregivers and pediatric patients, relatively, more events were experienced by pediatric patients. It is expected that pediatric patients will work with a caregiver particularly for the first use of the product.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall information density that contributed to these use errors. These use errors can contribute to the risk of overdose or inadvertent exposure of others, including symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Thus, additional mitigations could be implemented. See section 4.1.

• All three caregivers who made this use error still washed their hands. For caregivers, the exposure risk is minimized due to the completion of the hand-washing step. • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
Task: Wash hands <table border="1" data-bbox="348 751 747 906"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=9)</td><td>8 pediatric patients; 1 adult patient</td></tr> <tr> <td>CC (n=1)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=9)	8 pediatric patients; 1 adult patient	CC (n=1)		UD (n=0)		
Errors:	Participant Type:								
UE (n=9)	8 pediatric patients; 1 adult patient								
CC (n=1)									
UD (n=0)									
Observed use issue(s): • Use Errors: 9 participants did not wash their hands • Close Call: 1 participant did not initially wash his hands.									
Risk associated with Task Errors (Per Applicant URR): • The potential harm associated with these use issues include exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation.									
Relevant RCA/Subjective Feedback/Observation: Use Errors: • P3 did not wash her hands. P3 saw in the IFU during debrief to wash her hands and reported that the information was clear. The participant said she thought the product was like a "regular deodorant," which does not require hand washing. The Applicant attributed the root cause to negative transfer. • P7 and P15 did not read the instructions and did not wash their hands. During debrief, P15 commented that customers are typically just ready to open the box and use the product without									

referring to the instructions. The moderator prompted the participants to reference the instructions and perform a second use of the product. On the second use of the product, the participants did not wash their hands. P7 and P15 were prompted to look at Step 10: (b) (4) of the instructions and reported that the information was clear. P15 said that he had seen this information in the instructions previously but was focused on rinsing the applicator. During debrief, P7 said he thought this product was like a deodorant. The Applicant attributed the root cause to negative transfer.

- P8 did not read the instructions and did not wash her hands. P8 reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor about how to use it if that was an option for this type of product. The participant was prompted to perform a second use of the product using the instructions. On the second attempt, the participant washed her hands. The Applicant attributed the root cause to negative transfer.
- A5 did not wash her hands. A5 said she had seen the information in the instructions but ignored it. The participant said that she skips over the hand washing step in instructions frequently for other products. The Applicant attributed the root cause to negative transfer.
- P5 did not wash her hands. The participant reported that the information in Step 10: (b) (4) was clear. The participant said she may not have read that information the first time and suggested moving the information earlier in the instructions. The Applicant attributed the root cause to oversight of the information in the IFU.
- P13 did not wash her hands. P13 realized independently that she did not rinse off the applicator or wash her hands. The participant said she had not seen that information in the instructions because she was paying attention to the information on how to apply the product and did not read the rest of the instructions. The participant reported that the information in the instructions was clear. The Applicant attributed the root cause to oversight of information in the IFU.
- P1 did not wash his hands. The participant said he had seen the instructions but did not complete the step. The participant said he would normally wash his hands after using a medicated

product, but the study includes a placebo product. The participant reported that he saw Step 10: (b) (4), and that he understood he needed to rinse the cap and wash his hands. The Applicant attributed the root cause to study artifact. • P6 did not wash her hands. During debrief, P6 was asked what steps she should take after applying the gel. The participant read in the instructions that she should wash her hands. The participant said the instructions were clear, she just did not think about performing the task. The Applicant did not attribute a root cause. Close Call: • A13 initially did not use the instructions and did not wash his hands. Without moderator prompting during the simulated use scenario, the participant then identified and read the instructions, commenting "Oh, I did this wrong" and performed an additional use of the product. On the second use, A13 washed his hands. During debrief, A13 said the instructions informed him not to put the product on skin other than the underarms, which informed him he needed to wash his hands to remove any product that may have spread during application. The Applicant attributed the root cause to oversight of the IFU.	
Applicant Comment and Proposed Mitigations: • The amount of gel remaining on the hands after application should be minimal, particularly for users who apply the gel using the applicator. No gel should remain on the hands of any users who apply the gel correctly with the applicator as described within the IFU, indicating that there would be no exposure risk for these participants. For these reasons, the exposure risks are anticipated to be low. • The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. • The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) • When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. As such, we have determined that no	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find that the IFU can be improved to increase salience of critical task information and reduce overall information density that contributed to these use errors. These use errors can contribute to the risk of overdose or inadvertent exposure of others, including symptoms of local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation. Thus, additional mitigations could be implemented. See section 4.1.

additional changes to the user interface are needed to further address the use-related events.									
Task: Place Applicator and Cap Back on the Bottle <table border="1"> <tr> <td>Errors:</td><td>Participant Type:</td></tr> <tr> <td>UE (n=4)</td><td>4 pediatric patients</td></tr> <tr> <td>CC (n=1)</td><td>1 adult patient</td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=4)	4 pediatric patients	CC (n=1)	1 adult patient	UD (n=0)		
Errors:	Participant Type:								
UE (n=4)	4 pediatric patients								
CC (n=1)	1 adult patient								
UD (n=0)									
Observed use issue(s): - Use Errors: 3 participants did not place the applicator and cap back on the bottle. 1 participant did not put the cap back on the bottle. - Close Call: 1 participant did not initially put the applicator and cap back on the bottle.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation.									
Relevant RCA/Subjective Feedback/Observation: Use Errors: - P7, P8, P15 did not read the instructions and did not place the applicator and cap back on the bottle. During debrief, P7 commented that he thought the product was like a deodorant. P8 reported that she thought interacting with the product would be self-explanatory based on her experience with other prescription products. She also mentioned she would talk to the doctor about how to use it if that was an option for this type of product. P15 commented that customers are typically just ready to open the box and use the product without referring to the instructions. The moderator prompted the participants to reference the instructions and perform a second use of the product. On the second use of the product, the participants placed the applicator and cap back on the bottle. P15 noted that he would typically place the cap and applicator back on the bottle for storage. The Applicant attributed the root cause to negative transfer. - P6 placed the applicator back on the bottle but left the cap off. P6 reported she had seen this step in the instructions, but she did not put the cap on initially because she was not sure if she needed to do anything else with the applicator within the study session. The Applicant attributed the root cause to study artifact. Close Call:									

A13 initially did not use the instructions. The participant placed the pump back in the box but left the applicator and cap on the table. Without moderator prompting during the simulated use scenario, the participant then identified and read the instructions, commenting "Oh, I did this wrong" and performed an additional use of the product. On the second use, A13 placed the applicator and cap back on the bottle. The participant said the first use of the product he had not read the instructions, so he did not know the importance of the applicator. During the second use, he reassembled the product "for safe keeping." The Applicant attributed the root cause to oversight of the IFU.									
Applicant Comment and Proposed Mitigations: - The amount of gel remaining on the applicator should be minimal after application, particularly after the gel is dry (within a few minutes of use). Therefore, the exposure risks are anticipated to be low. - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - When referring to the instructions, participants were able to comprehend the information for this step. This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
Knowledge Task Assessment 1: Identify Intended Users <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=1)</td><td>1 adult patient</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=1)	1 adult patient	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=1)	1 adult patient								
CC (n=0)									
UD (n=0)									
Observed error(s): 1 participant reported he would expect multiple people to be able to use the same product.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include									

exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation.									
Relevant RCA/Subjective Feedback/Observation: A1 (use error) reported that he would expect multiple people to be able to use the same product. The moderator then directed the participant to review the instructions. The participant read (b) (4) and reported that he then understood that only people who have a prescription for the product should use it. This participant's mental model indicated that topical gel/deodorant products could be used by multiple people. The Applicant attributed this root cause to mental model.									
Applicant Comment and Proposed Mitigations: - Participants may be more likely to see this information during actual use while working through the workflow. Comprehension questions are out of context of the current task, making it sometimes more difficult to identify the information. - The (b) (4) information is displayed on the front panel of the instructions. - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) (b) (4) to help promote successful use by stating (b) (4) - When referring to the instructions, the participant was able to comprehend the information for this step. - This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
Knowledge Task Assessment 2: Identify the Gel should be Applied before Bed. <table border="1"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=0)</td><td></td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=3)</td><td>3 caregivers</td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=0)		CC (n=0)		UD (n=3)	3 caregivers	
Errors:	Participant Type:								
UE (n=0)									
CC (n=0)									
UD (n=3)	3 caregivers								
Observed issue(s): 3 participants initially reported to apply at incorrect time of day.									

Risk associated with Task Errors (Per Applicant URR): The potential harm associated with these use issues include underdose.	
Relevant RCA/Subjective Feedback/Observation: - C7 initially reported that she assumed the gel should be applied in the morning. Unprompted, she then looked at the instructions and then saw in Step 2: (b) (4) that the gel should be applied before bed. The participant reported that she initially assumed the gel would be like other antiperspirants that are applied at the beginning of the day. The Applicant attributed the root cause to negative transfer. - C8 initially answered that the gel should be applied in the morning and reported this is because she assumed she would use the product when getting ready for the day after a shower. Unprompted, the participant then looked at the instructions and saw to wait 8 hours after showering (b) (4) which indicated to the participant that the gel should be applied at the end of the day. When prompted to look at Step 2: (b) (4) in the instructions, the participant said the information was clear, but she had not seen it previously. The Applicant attributed the root cause to mental model. - C13 initially reported that the gel should be applied in the morning while reviewing the IFU. Unprompted, the participant then continued to refer to the IFU and reported that the gel should be applied before bed. The participant reported he was initially focused on the timing requirements section of the IFU (apply 30 minutes after showering, 8 hours after shaving, etc.) and not the time of day the gel should be applied. He said that he initially thought the gel could be applied in the morning since he showers in the morning, and he would apply the gel 30 minutes after his shower. The Applicant attributed the root cause to oversight of information.	
Applicant Comment and Proposed Mitigations: - The efficacy of the drug is greater at 15%, but efficacy has still been clinically observed from the 5% sofpironium bromide strength in the following contexts: - o ECCLOCK[®], which is a commercially available product on the market in Japan, at 5% sofpironium bromide content. - o Phase 2 safety and efficacy study of 5%, 10%, and 15% gel (BBI-4000-CL-203).	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.

- The product workflow is aligned with other underarm products on the market. Drysol is a commercially available antiperspirant that also instructs users to apply the product at bedtime. - Participants may be more likely to see this information during actual use while working through the workflow. Comprehension questions are out of context of the current task, making it sometimes more difficult to identify the information. - The front of the bottle labeling states that intended users should (b) (4) - The IFU also describes that intended users should (b) (4) in multiple locations (front panel and (b) (4) (b) (4)) - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - When referring to the instructions, participants were able to comprehend the information for this step. (Step 2 (b) (4)) - This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
Knowledge Task Assessment 3: Identify Users should wait 8 hours before Applying the Gel. <table border="1" data-bbox="348 1076 747 1200"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=0)</td><td></td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=1)</td><td>1 pediatric patient</td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=0)		CC (n=0)		UD (n=1)	1 pediatric patient	
Errors:	Participant Type:								
UE (n=0)									
CC (n=0)									
UD (n=1)	1 pediatric patient								
Observed error(s): 1 participant initially reported that if the product was used within the last 8 hours, the product should not be used again within the 8 hours.									
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with this use issue is overdose or an underdose due to possible drug interactions between the									

proposed product and another product applied.	
Relevant RCA/Subjective Feedback/Observation: P10 initially reported that if he had used this product within the last 8 hours, the product should not be used again within the 8 hours. The participant then chose to review the instructions without prompting, at which point he reported that the product should not be used within 8 hours of using other underarm products. The Applicant attributed the root cause to mental model.	
Applicant Comment and Proposed Mitigations: - For underdose, the efficacy of the drug is greater at 15%, but efficacy has still been clinically observed from the 5% sofipirionium bromide strength in the following contexts: - ECCLOCK[®], which is a commercially available product on the market in Japan, at 5% sofipirionium bromide content. - Phase 2 safety and efficacy study of 5%, 10%, and 15% gel (BBI-4000-CL-203). - For overdose, BBI has conducted two clinical studies that demonstrate that a one-time dose 6-fold above the therapeutic dose did not cause a meaningful increase in any adverse events (BBI-4000-CL-106: QT prolongation study, BBI-4000-CL-109: pharmacokinetics and dose safety study). In addition, a clinical drug-drug interaction study (BBI-4000-CL-104) demonstrated that any drug interactions between the SB Combination Product and other products applied would not likely result clinically meaningful increases systemic sofipirionium concentrations. - The IFU describes that intended users should not apply the product if deodorant has been applied within the last 8 hours (Step 4 (b) (4)) - Participants may be more likely to see this information during actual use while working through the workflow. Comprehension questions are out of context of the current task, making it sometimes more difficult to identify the information. Additionally, having an understanding of when other products can be applied is out of context of the standard use workflow; this information would only be needed in the instance where the user is considering application of another product. - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading “STOP!” with a red stop sign graphic	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.

and text underneath “You MUST read the instructions” was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - When referring to the instructions, participants were able to comprehend the information for this step (Step 4 (b) (4)) - This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.									
Knowledge Task Assessment 4: Identify that the Pump does not need to be Primed for a Second Time Use <table border="1"> <tr> <td>Errors:</td><td>Participant Type:</td></tr> <tr> <td>UE (n=3)</td><td>1 adult patient; 1 pediatric patient; 1 caregiver</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=3)	1 adult patient; 1 pediatric patient; 1 caregiver	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=3)	1 adult patient; 1 pediatric patient; 1 caregiver								
CC (n=0)									
UD (n=0)									
Observed error(s): 3 participants stated priming should occur before each use.									
Risk associated with Task Errors (Per Applicant URR): No potential harm associated with these use issues.									
Relevant RCA/Subjective Feedback/Observation: - P5 reported that priming the pump should occur during each use of the product without referring to the instructions. Then the participant was prompted to review the instructions, at which point she reported that priming is for first use only. The participant said she was focused on the information about washing the gel down the sink and thought she needed to do so every time she used the product. The Applicant attributed the root cause to oversight of information. - C13 did not look at the instructions while answering the question and said that priming should occur during each use of the product. During debrief, the participant looked at the instructions and answered correctly. The participant said he felt the information was clear. The participant described that he would not want to waste medicine, so after gaining experience with the product, if the pump seemed like it was still “loaded” for each									

use, he would not continue to pump gel into the sink. The Applicant attributed the root cause to mental model. A13 thought the pump should be primed before each use. A13 reported that prior experience with pump products informed him that the pump should be primed before each use. After reviewing the instructions and the video, the participant still thought priming was required for every use. The Applicant attributed the root cause to negative transfer.									
Applicant Comment and Proposed Mitigations: - There are no critical risks associated with the error of priming before each use. - Participants may be more likely to see this information during actual use while working through the workflow. Comprehension questions are out of context of the current task, making it sometimes more difficult to identify the information. Additionally, having an understanding of whether the product should be primed for subsequent uses is out of context of the use workflow evaluated; this information would only be needed in the instance where the user is considering a second application of the product. - When referring to the instructions, participants were able to comprehend the information for this step. - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading “STOP!” with a red stop sign graphic and text underneath “You MUST read the instructions” was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
Knowledge Task Assessment 5: Identify Users should wait 5 minutes before Putting on Clothing <table border="1" data-bbox="348 1281 747 1401"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=0)</td><td></td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=1)</td><td>1 caregiver</td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=0)		CC (n=0)		UD (n=1)	1 caregiver	
Errors:	Participant Type:								
UE (n=0)									
CC (n=0)									
UD (n=1)	1 caregiver								

Observed error(s): 1 participant initially reported that he would need to keep the patient's shirt away from the underarms after applying the product but did not state a time.	
Risk associated with Task Errors (Per Applicant URR): The potential harm associated with this use issue includes exposure risk which could lead to local site reaction, transient mydriasis, blurred vision dry mouth, and urinary hesitation.	
Relevant RCA/Subjective Feedback/Observation: C11 initially reported based on the instructions that he would need to keep the patient's shirt away from the underarms after applying the product but did not specify for how long. C11 then reviewed the instructions again and saw to keep clothing away from the underarms for 5 minutes. The participant reported that he had initially skipped this information in the instructions. The Applicant attributed the root cause to oversight of information.	
Applicant Comment and Proposed Mitigations: - The participant understood that the waiting step was needed, such that this participant would still wait some amount of time prior to applying clothing, which minimizes the risk of exposure from wet gel onto their clothing. - Participants may be more likely to see this information during actual use while working through the workflow. Comprehension questions are out of context of the current task, making it sometimes more difficult to identify the information. - When referring to the instructions, the participant was able to comprehend the information for this step. - The carton and bottle labeling emphasize the importance of thoroughly referring to the instructions for use to help promote successful use. Text reading "STOP!" with a red stop sign graphic and text underneath "You MUST read the instructions" was added on the top flap of the carton, on the primary panel of the carton, and on the front bottle label. - The carton, bottle, and IFU (b) (4) to help promote successful use by stating (b) (4) - This demonstrates the effectiveness of the IFU. As such, we have determined that no additional changes to the user interface are needed to further address the use-related events.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.

APPEARS THIS WAY ON ORIGINAL

4 CONCLUSION AND RECOMMENDATIONS

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, we note 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. We acknowledge the additional mitigations implemented post-validation; however, our review of the provided root cause and subjective feedback and our evaluation of the proposed user interface, proposed packaging, label, and labeling identified areas of vulnerability that may lead to medication errors. We provide our recommendations for [Botanix SB, Inc.](#) related to the HF validation study in Section 4.1 below. We recommend 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.

4.1 RECOMMENDATIONS FOR BOTANIX SB, INC.

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, we note 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. We acknowledge the additional mitigations implemented post-validation; however, our review indicates that additional risk mitigations are necessary. Therefore, you should:

1. Review the HF study results and subjective feedback to identify potential areas of optimization.
2. Implement additional design modifications and user interface revisions identified in item #1 above, along with the following:
 - a. Label the applicator with the applicator's intended use/purpose because several users in the HF validation study indicated that they did not understand what the applicator was, or how to use it.
 - b. Revise the instructions for use (IFU) to address the subjective feedback that:
 - i. The IFU has too much information
 - ii. Certain information in the IFU lacks salience
 - iii. The IFU was folded which may have contributed to missed steps
 - c. Place the statement "wash hands with soap and water immediately after use" on the principal display panel of the carton and container labeling to emphasize this important information, based on the residual risk and subjective feedback related to the task of washing hands.
3. Consider implementing a mitigation to address the foreseeable use issue of users of this product tilting the applicator to apply to the underarm(s) and spilling the gel, as observed in the HF validation study.
4. Conduct another HF validation study to demonstrate that the revised user interface supports the safe and effective use of the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Sofpironium bromide that Botanix SB, Inc. submitted on [9/23/2022](#).

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Active Ingredient (Drug or Biologic)	sofpironium bromide
Indication	indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older
Route of Administration	topical
Dosage Form	topical gel
Strength	15%
Dose and Frequency	Apply 1 pump of sofpironium bromide gel, 15% per underarm once a day at bedtime
How Supplied	supplied in an airless bottle sealed with a multi-dose metered pump, applicator, and cap. Each bottle contains 50 mL of gel with a multi-dose pump capable of dispensing 60 pump actuations.
Storage	Store upright at room temperature of 20°–25°C (68°–77°F); brief excursions permitted to 15°–30°C (59°–86°F) [See USP Controlled Room Temperature]. Sofpironium bromide gel, 15% is flammable; keep away from heat or flame
Container Closure/Device Constituent	Multi-dose metered pump (See figure 1)
Intended Users	Patients; Caregivers
Intended Use Environment	Home

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 16, 2022, we searched the L:drive and AIMS using the terms, NDA 217347 and sofpironium bromide to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 1 previous review^b, and we confirmed that our previous recommendations were implemented.

APPEARS THIS WAY ON ORIGINAL

^b Oguntimein, O. HF Validation Study Protocol Review for sofipirionium bromide (IND 121256). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2021-2263.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\nda217347\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pah\5354-other-stud-rep\human-factors\prpt-21-018-bbi-hfe-ue-summary-rpt.pdf>

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\nda217347\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pah\5354-other-stud-rep\human-factors\prpt-21-018-bbi-hfe-ue-summary-rpt.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

Applicant's February 17, 2023 IR response to the Agency's February 7, 2023 IR:

<\\CDSESUB1\EVSPROD\nda217347\0009\m1\us\111-information-amendment\1113-clin-info-amend.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following sofipironium bromide labels and labeling submitted by Botanix SB, Inc..

- Container label received on September 23, 2022
- Carton labeling received on September 23, 2022
- Instructions for Use received on September 23, 2022, available from <\\CDSESUB1\EVSPROD\nda217347\0001\m1\us\114-labeling\draft\labeling\instructions-for-use.pdf>

F.2 Label and Labeling Images

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

MATTHEW J BARLOW
09/15/2023 03:52:53 PM

JASON A FLINT
09/15/2023 04:12:18 PM

MISHALE P MISTRY
09/15/2023 04:31:24 PM

Clinical Inspection Summary

Date	06/02/2023
From	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Roselyn Epps, MD, Clinical Reviewer David Kettl, MD, Clinical Team Leader Craig Johnson, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	217347
Applicant	Botanix SB, Inc.
Drug	Sofpironium bromide
NME (Yes/No)	Yes
Therapeutic Classification	Anticholinergic
Proposed Indication	For topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older
Consultation Request Date	11/21/2022
Summary Goal Date	06/23/2023
Action Goal Date	08/30/2023
PDUFA Date	09/23/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Botanix SB, Inc., submitted clinical data from Study BBI-4000-CL-301/CARDIGAN 1 (NCT03836287) and Study BBI-4000-CL-302/CARDIGAN 2 (NCT03948646) to support a New Drug Application (NDA 217347) for sofpironium bromide for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.

Four clinical investigators (Drs. Alen, Fitzgerald, Sullivan, and Smith) were inspected. Despite the inspections of Drs. Fitzgerald, Sullivan, and Smith 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.

II. BACKGROUND

The proposed indication for sofpironium bromide gel, 15% is “for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age or older.” The gel is applied to the underarms daily at bedtime.

Two multicenter, randomized, double-blinded, vehicle-controlled, pivotal phase 3 studies were performed in the US for safety and efficacy:

- CARDIGAN 1
- CARDIGAN 2

There were two co-primary efficacy endpoints for each study:

- Proportion of subjects having at least a 2-point improvement in the Hyperhidrosis Disease Severity Measure-Axillary 7 (HDSM-Ax-7) scale score from Baseline to EOT, i.e., responders
- Change in continuous gravimetric sweat production (GSP) from Baseline to EOT

For the HDSM-Ax-7 endpoint, the EOT assessment at Visit 12 (Day 43±2) was compared to the Baseline Assessment at Visit 4/Day 1.

For Baseline GSP, the median of the GSP1, GSP2, and GSP3 measurements obtained during Visits 2-4 was used. For EOT GSP, the median of GSP4, GSP5, and GSP6 measurements obtained during Visits 10-12 was used.

Key eligibility criteria included:

- Males or females ≥9 years of age in general good health
- HDSM-Ax-7 of 3-4, inclusive, at Screening (Visit 1) and Baseline (Visit 4)
- Gravimetric test indicating a minimum of 50 mg of sweat production at rest in each axilla, with a 2-axilla combined total of at least 150 mg of sweat production, in 5 minutes at room temperature (20 to 25°C or 68 to 77°F) at Visit 1 and at least one of Visits 2, 3, and 4.
- Symptoms for ≥6 months
- No known cause of hyperhidrosis

Subjects were randomized 1:1 to receive sofpironium bromide gel, 15% or vehicle gel on Day 1/Visit 4 after final screening and eligibility was confirmed. The subjects applied the investigational medicinal product (IMP) once daily at bedtime to each axilla for 42 consecutive days. Each subject had a total of 13 scheduled visits over approximately 11-15 weeks, inclusive of the screening visits.

In CARDIGAN 1, 38 sites screened at least one subject, and 35 sites randomized at least one subject. All sites were in the U.S. With respect to subjects, 173 subjects received sofpironium bromide gel, and 176 subjects received the vehicle.

In CARDIGAN 2, 42 sites screened at least one subject, and 33 sites randomized at least one subject. All sites were in the U.S. With respect to subjects, 180 subjects received sofipironium bromide gel, and 171 subjects received the vehicle.

RESULTS

1. Dr. Zoila Alen (Site 1016)

7751 W 28th Ave Unit 6
Hialeah, FL 33016-5113

Inspection Dates: 2/15/2023 – 2/17/2023

This investigator was inspected as a routine PDUFA inspection for CARDIGAN 1. This was the first FDA inspection of this investigator.

For CARDIGAN 1, there were 23 subjects screened; 21 subjects were enrolled and randomized (two screen failures). All subjects completed the study.

Subject source records for all 21 enrolled subjects were reviewed. These records included: electronic case report forms (eCRFs) and paper source documents for informed consent (ICF) and assent, medical history, inclusion/exclusion information, AEs, and concomitant medications. Printouts of GSP readings and study visit progress notes were also reviewed.

Study-related records reviewed included: the protocol; subject enrollment log; Clinical Laboratory Improvements Amendments (CLIA) certificate for the central laboratory; Institutional Review Board (IRB) approvals and correspondence; financial disclosures; site training log; delegation log; master protocol deviation log; study staff curricula vitae; documents for receipt, storage, and disposition of the IMP; and sponsor correspondence and monitoring activities.

For verification of the primary endpoint data, the submitted data line listings were compared to source data at the site. For all 21 enrolled subjects, the eCRFs were reviewed to verify the HDSM-Ax-7 questionnaire endpoint data. The source data for GSP were also reviewed for the 21 enrolled subjects. No discrepancies were identified.

The site was chosen for inspection because no AEs were reported. The inspection found no unreported AEs or SAEs in the study subject source records.

2. Dr. Tory P. Sullivan (Site 1004)

16100 NE 16th Ave Ste A
North Miami Beach, FL 33162-4708

Inspection Dates: 2/27/2023 – 3/3/2023

This investigator was inspected as a routine PDUFA inspection for CARDIGAN 1. The investigator was last inspected 3/15/2018 without significant findings.

For CARDIGAN 1, 29 subjects were screened; 21 subjects were enrolled and randomized (eight screen failures). Twenty subjects completed the study; the mother of the sole minor subject withdrew consent after the EOT visit.

Subject source records for the 21 enrolled subjects that were reviewed included: eCRFs, medical history forms, inclusion/exclusion information, AE log, concomitant medication log, printouts of GSP weights affixed to GSP source documents, laboratory reports, IMP dispensing and return log, IMP Application Compliance log, and specific visit source records. In addition, all 29 screened subjects' ICFs and assent forms (as applicable) were reviewed.

Study-related records reviewed included: the protocol; IRB approvals and correspondence; master protocol deviation list, CLIA certificate for the central laboratory; financial disclosures; site training activities; records related to receipt, storage, and disposition of the IMP; and sponsor correspondence and monitoring activities.

The submitted data listings for efficacy were compared to source records for verification of the primary efficacy endpoint data. The eCRFs and GSP source documents were reviewed for all 21 enrolled subjects to verify the results for HDSM-Ax-7 and GSP, respectively. Dermatology Life Quality Index (DLQI) questionnaire results were also verified. No discrepancies were identified.

The following protocol deviations related to efficacy and local tolerability assessments were identified at the site; some were not reported in the submission. The clinical investigator failed to have the subject complete one or more efficacy endpoint data questionnaires for one or more study visits according to the protocol, shown in the following table:

Table 1: Missing Subject Questionnaires (Efficacy)

Subject number	Visit Number/Date	Questionnaire(s) Not Done	Reported as a Protocol Deviation
(b) (6)	Visit 13 on (b) (6)	HDSM-Ax-7	No
	Visit 12 on (b) (6)	DLQI	No
	Visit 12 on (b) (6)	DLQI	Yes
	Visit 7 on (b) (6)	HDSM-Ax-7	Yes
	Visit 6 on (b) (6)	HDSM-Ax-7 and DLQI	No
	Visit 6 on (b) (6)	DLQI	Yes
	Visit 12 on (b) (6)	DLQI	

The clinical investigator failed to conduct GSP assessments during the protocol-specified window of 7:00 am – 11:00 am in two out of 21 randomized subjects:

- Subject (b) (6), Visit 11 on (b) (6) (completed at 11:29 am); reported as a protocol deviation
- Subject (b) (6), Visit 5 on (b) (6) (completed at 11:03 am); not reported as a protocol deviation

In at least three instances involving two subjects, the clinical investigator did not conduct the Investigator's Local Tolerability Assessment *after* the subject questionnaires were completed, as required by the protocol. None were reported as protocol deviations:

- Subject (b) (6), Visit 12 on (b) (6)
- Subject (b) (6), Visit 4 on (b) (6) and Visit 12 on (b) (6)

The site also failed to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation in five out of 21 subjects. GSP weights for Subject (b) (6) at Visit 9 were not attributable (not signed). Other regulatory violations included inadequate documentation of concomitant medications, safety assessment time points, AEs or AE review, medical histories, and timely safety lab review. However, there was no under-reporting of AEs.

Reviewer's comments: We note that none of missing subject efficacy questionnaires (Table 1) corresponded to a timepoint relevant to the HDSM-Ax-7 co-primary endpoint (Visit 4 and Visit 12) and DLQI did not contribute to a primary endpoint. We also note that a slightly delayed EOT GSP in a single subject is unlikely to cause a significant change in the study results as the study had 350 subjects in the Intent-To-Treat efficacy population. Finally, we note that the three instances of the Investigator's Local Tolerability Assessment not being completed after the subject questionnaires are unlikely to impact the safety assessment of the product.

The clinical investigator acknowledged the protocol deviations and documentation failures and instituted corrective and preventive actions (CAPA). The CAPA appears to be acceptable.

3. Dr. Maryellen Fitzgerald (Site 2052)

521 Mount Auburn St Ste 200
Watertown, MA 02472-4153

Inspection Dates: 3/7/2023 – 3/10/2023

This investigator was inspected as a routine PDUFA inspection for CARDIGAN 2. This was the first FDA inspection of this investigator.

For CARDIGAN 2, 48 subjects were screened; 24 subjects were enrolled and randomized (24 screen failures). Nineteen subjects completed the study: two subjects were lost to follow-up, and three subjects withdrew consent or discontinued following an AE which was reported.

Subject source records reviewed included: ICFs, inclusion/exclusion checklists, visit-specific worksheets, vital sign and physical exam worksheets, IMP dispensing and randomization records, GSP instrument printouts, GSP Source and Local Tolerability worksheets, and eCRFs (for HDSM-Ax-7). Source records for all 24 enrolled subjects were reviewed.

Study-related records reviewed included: sponsor/monitor correspondence, monitoring visit follow-up letters, training documentation, IRB approvals, financial disclosure declarations,

delegation of authority log, and IMP accountability records.

There was no under-reporting of AEs. No significant discrepancies between the information reported in the data listings and the efficacy source data were identified.

There were twelve subjects who had Visits 10-12 (EOT) that were delayed or out-of-window due to site logistics issues or “subject’s unavailability”, all of which were reported to the FDA.

Table 2: Out-of-Window EOT Visits (Visits 10-12)

Subject Number Arm	Out- of-Window Visits	Day(s) out of Window
(b) (6) Vehicle	Visit 10 Visit 11 Visit 12	11 12 12
(b) (6) Sofipirionium Bromide Gel	Visit 10 Visit 11 Visit 12	7 7 11
(b) (6) Vehicle	Visit 10 Visit 11 Visit 12	2 2 5
(b) (6) Sofipirionium Bromide Gel	Visit 12	5
(b) (6) Vehicle	Visit 10 Visit 11 Visit 12	1 1 4
(b) (6) Sofipirionium Bromide Gel	Visit 11 Visit 12	5 5
(b) (6) Vehicle	Visit 12	3
(b) (6) Vehicle	Visit 11 Visit 12	6 6
(b) (6) Vehicle	Visit 12	5
(b) (6) Sofipirionium Bromide Gel	Visit 10 Visit 11 Visit 12	1 1 5
(b) (6) Vehicle	Visit 12	2
(b) (6) Vehicle	Visit 10 Visit 11 Visit 12	5 5 5

For the above subjects, treatment ended the day before Visit 12, resulting in a longer duration of treatment when the visit was out-of-window. Generally, there was a lack of documentation as to why visits were out-of-window (e.g., subject availability, COVID-related, weather, or

issues at the clinical site). The clinical investigator explained that some out-of-window visits were caused because Visit 12 would have occurred on a Friday, and it was the site's policy that visits requiring lab samples to be shipped to a central laboratory could not be scheduled on Fridays or the weekend due to shipping and pick-up issues. Therefore, the visit was postponed. Other visits were delayed due to subject availability.

Reviewer comments:

- *At least 12 out of 24 enrolled subjects (50%) had out-of-window (delayed) visits for at least one visit between Visit 10-12; all were reported as protocol deviations in the submission.*
- *Although Visits 10-12 were important for the HDSM-Ax-7 primary endpoint (Visit 12) and the GSP primary endpoint (Visits 10-12), these delays are unlikely to impact efficacy assessments. The out-of-window visits occurred in both arms. Although the delays resulted in longer treatment times, there is no treatment duration specified in the proposed prescribing information.*
- *Some of these delays appear to be related to site-specific limitations (inability to ship labs on a Friday resulting in postponed visits). Information related to these out-of-window visits was conveyed to the primary clinical reviewer on 4/4/2023 by email.*
- *The clinical investigator submitted a CAPA consisting of staff education and weekly meetings to minimize out-of-window visits in the future. Special attention will be given to visits falling on Fridays that require laboratory samples. The site will also inform the sponsor of any protocol deviations related to lab pick-up issues. The CAPA appears to be acceptable.*

4. Dr. Scott A. Smith (Site 2051)

13512 E Mansfield Ave
Spokane Valley, WA 99216

Inspection Dates: 3/20/2023 – 3/22/2023

This investigator was inspected as a routine PDUFA inspection for CARDIGAN 2. This was the first FDA inspection of this investigator.

For CARDIGAN 2, 13 subjects were enrolled and treated at the site. All subjects completed the study. Subject-related source records were reviewed for all 13 subjects and included: documentation of informed consent, eligibility criteria, AEs, protocol deviations, physical examinations, treatment with the IMP, subject visits, tolerability assessments, GSP, and HDSM-Ax-7.

Study-related documents reviewed included ethics committee approvals, documentation of training and certifications, communications, and monitoring activities.

The source data were compared to the provided line listings. No unreported protocol deviations were identified. One discrepant GSP result between the source documentation and the sponsor-provided line listings was identified. For Subject (b) (6) at Visit 4, the right axilla GSP weight in the source data was recorded as 57.5 mg, but in the eCRF it was recorded

as 95.7 mg.

Reviewer comment: This discrepancy had no impact on the subject's eligibility or assessing the subject's change in GSP from Baseline because, for Baseline GSP, the median of the total GSP results from Visits 2-4 were to be used. For Subject (b) (6), the Baseline GSP result came from Visit 2 (i.e., Visit 2's total GSP result was the median for Visits 2-4).

There were two unreported AEs. Subjects (b) (6) and (b) (6) were noted to have "sickness" or "illness" in progress notes that resulted in out-of-window visits for Visit 5, but no AEs were recorded. The out-of-window visits were recorded as protocol deviations. No further information on the subjects' "sickness" or "illness" was documented in the source records.

Reviewer comments:

- There was no detailed information regarding "sickness" or "illness" to assess the impact on the safety profile of the study drug. However, these were isolated events.*
- In response to this observation, the clinical investigator reported being unclear as to which AEs were to be reported. In the future, the clinical investigator would contact the sponsor or medical monitor if there were confusion about AE reporting. The response appears to be acceptable.*

{See appended electronic signature page}

Stephanie Coquia, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

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/s/

STEPHANIE F COQUIA
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MICHELE B FEDOWITZ
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JENN W SELLERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 2, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217347
Product Name, Dosage Form, and Strength:	sofpironium topical gel, 12.45% ^a
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Botanix SB Inc. (Botanix)
FDA Received Date:	September 23, 2023
TTT ID #:	2022-1828
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

^a We note the Applicant submitted the established name, dosage form, and strength as 'sofpironium bromide, 15%'. However, per Office of Pharmaceutical Quality (OPQ), established name, dosage form, and strength is 'sofpironium topical gel, 12.45%'.

1. REASON FOR REVIEW

As part of the approval process for sofpironium topical gel, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed sofpironium topical gel prescribing information (PI), Instructions for Use (IFU), Patient Prescribing Information (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Instructions for Use (IFU), Patient Prescribing Information (PPI), container label, and carton labeling. We find the label and labeling can be improved to facilitate product identification and prevent wrong dose and deteriorated drug errors. Note that DMEPA 1 is also evaluating the Human Factors (HF) validation study results under separate cover and additional label and labeling comments may be forthcoming based on the outcome of that review.

4. CONCLUSION & RECOMMENDATIONS

We concluded that the proposed label and labeling can be improved, and we provided recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. General Comments

1. We recommend the placeholder, “TRADENAME” be removed throughout the labels and labeling once a new name is found conditionally acceptable.

B. Prescribing Information

1. Dosage and Administration Section

(b) (4)

2. Dosage Forms and Strengths Section

- a. Consider revising (b) (4)

(b) (4)

3. How Supplied/Storage and Handling Section

- a. Consider adding the following statement “Each pump actuation (b) (4)
0.67 mL of gel (b) (4)

4.2 RECOMMENDATIONS FOR BOTANIX SB INC. (BOTANIX)

We recommend the following be implemented prior to approval of this NDA 217347

A. General Comments (Container labels & Carton Labeling)

1. Once a proprietary name is found conditionally acceptable, the placeholder “Tradename” must be replaced with the proprietary name on the container labels and carton labeling and the revised labels and labeling must be submitted to the Agency for review.
2. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2). Additionally, the established name lacks prominence on the principal display panel (PDP). We recommend increasing the prominence of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. The strength statement lacks prominence. Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by

reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.).

4. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read (b) (4)
Dosage: See prescribing information.”
5. Revise the statement (b) (4) to read: “Each pump actuation delivers 0.67 mL of gel containing 72 mg of sofipironium”.
6. Relocate the statement (b) (4) capable of dispensing 60 pump actuations” and place it underneath “each pump actuation delivers 0.67 mL of gel containing 72 mg of sofipironium”.
7. Revise the net quantity to “50 mL” and relocate to the bottom of the principal display panel (PDP).

B. Container Labels

1. We recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode. Consider orienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.^b
2. Consider moving the statement: “Warnings: Gel is flammable. Avoid (b) (4) flame, or smoking until gel has dried” from the principal display panel to the side panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for sofpironium topical gel received on September 23, 2022, from Botanix SB Inc. (Botanix).

Table 2. Relevant Product Information for sofpironium topical gel	
Initial Approval Date	N/A
Active Ingredient	sofpironium bromide
Indication	topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.
Route of Administration	topical
Dosage Form	topical gel
Strength	15%
Dose and Frequency	1 pump actuation per underarm administered topically once a day at bedtime, for a daily dose of 174 mg of sofpironium bromide.
How Supplied	Supplied in an airless bottle sealed with a multi-dose metered pump, applicator, and cap. Each bottle contains 50 mL of gel with a multi-dose pump capable of dispensing 60 pump actuations.
Storage	Store upright at room temperature of 20°–25°C (68°-77°F); brief excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].
Container Closure	airless bottle sealed with a multi-dose metered pump, applicator, and cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 7, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 'sofpironium bromide'. Our search identified one previous review^c, and we confirmed that our previous recommendations were implemented.

APPEARS THIS WAY ON ORIGINAL

^c Oguntimein M. Human Factors Validation Study Protocol Review for Sofpironium bromide (IND 121256). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JAN 10. RCM No.: 2021-2263.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following sofipirionum topical gel label and labeling submitted by Botanix SB Inc. (Botanix).

- Container label received on September 23, 2022
- Carton labeling received on September 23, 2022
- Prescribing Information (Image not shown) received on September 23, 2022 available from <\\CDSESUB1\EVSPROD\nda217347\0001\m1\us\114-labeling\draft\labeling\draft-label.pdf>
- Instructions for Use (Image not shown) received on September 23, 2022 available from <\\CDSESUB1\EVSPROD\nda217347\0001\m1\us\114-labeling\draft\labeling\instructions-for-use.pdf>
- Patient Prescribing Information (Image not shown) received on September 23, 2022 available from <\\CDSESUB1\EVSPROD\nda217347\0001\m1\us\114-labeling\draft\labeling\patient-information.pdf>

F.2 Label and Labeling Images

Container Label

2 Pages of Draft Labeling have been Withheld in Full as
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^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

PEGGY M RAHBANI
05/02/2023 02:47:38 PM

MADHURI R PATEL
05/03/2023 12:49:21 PM

Interdisciplinary Review Team for Cardiac Safety Studies
QT Study Review

Submission	NDA 217347
Submission Number	0001
Submission Date	9/23/2022
Date Consult Received	10/7/2022
Drug Name	Sofpironium bromide
Indication	Treatment of primary hyperhidrosis - Axillary
Therapeutic Dose	1 pump sofipironium bromide gel (15%) per underarm once a day at bedtime
Clinical Division	DDD
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 10/7/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND 121256 dated [08/04/2016](#); [11/27/2018](#) in DARRTS;
- Study report for BBI-4000-CL-106 (NDA 217347 / eCTD 0001; [link](#));
- Study report for BBI-4000-CL-104 (NDA 217347 / eCTD 001; [link](#));
- Study report for BBI-4000-CL-102 (NDA 217347 / eCTD 001; [link](#));
- Cardiac Safety Report (NDA 217347 / eCTD 0001; [link](#));
- Investigator's brochure (NDA 217347 / eCTD 0001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (NDA 217347 / eCTD 0001; [link](#)).

1 SUMMARY

Sofpironium bromide did not prolong the QTcF interval in this Thorough QT study – see Table 1 for overall results.

Clinical study BBI-4000-CL-106 was a four-way, crossover, randomized, double-blind, placebo- and active-controlled study to evaluate the effect of a single therapeutic or suprathreshold dose of sofipironium 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 $\Delta\Delta\text{QTc}$ (section 4.5) and no outliers in categorical analysis (section 4.4).

Table 1: Summary of findings

QT assessment pathway	☒ Thorough QT study ☐ Substitute for thorough QT study (5.1) ☐ Alternative QT study when a thorough QT study is not feasible (6.1)				
Clinical QT study findings	ECG parameter	Treatment	Time (h)	$\Delta\Delta QTcF$ (msec)	90% CI (msec)
	QTc	Sofpironium bromide 15% 173 mg	1.0	3.5	(2.0 to 4.9)
	QTc	Sofpironium (Occluded) 1038 mg	1.0	0.8	(-0.6 to 2.2)
In vitro findings	Integrated nonclinical risk assessment was not conducted since the QT assessment pathway is a thorough QT study.				
In vivo findings					

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Based on the results of our independent analysis, we agree that there is a low risk of QTc prolongation associated with administration of sofipironium bromide gel (15%) at the proposed dosing regimen.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0001 ([link](#)) from the CSS-IRT

Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At an exposure 3 times the exposure associated with the maximum approved recommended dose, sofipirionium does not prolong the QTc interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

Sofipirionium bromide gel, 15%, is an anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. The therapeutic dose is one pump/actuation per underarm at bedtime to deliver sofipirionium 174 mg once a day.

The sponsor initially proposed a substitute for a thorough QT study, which we did not agree to ([review](#)). The sponsor subsequently submitted a TQT study protocol which was not changed significantly since review.

3.1.1 Clinical pharmacology

Sofipirionium bromide gel is absorbed with a Tmax ranging from 4 – 16 hours and has a mean half-life of approximately 6 hours. In clinical studies, sofipirionium exposure was affected by the administration of inhibitors of CYP2D6, CYP3A4, OCT2, MATE1, or MATE2-K. However, due to low systemic sofipirionium exposure observed following topical administration, dose adjustment of sofipirionium bromide gel, 15% is not required with concomitant administration of CYP2D6, CYP3A4, OCT2, MATE1, and MATE2-K inhibitors. The impact of hepatic or renal impairment on sofipirionium PK has not been evaluated.

In Study BBI-4000-CL-102, the geometric mean Cmax was 0.487 ng/mL in participants who were administered the therapeutic dose (i.e., 174 mg in cohort A) of sofipirionium bromide gel, under arms, once daily for 21 days. In a maximal use cohort of the study (cohort B), a suprathapeutic dose of 522 mg was applied to diseased and none-diseased sites (i.e., axilla, palms, and soles) and provided steady state geometric Cmax of 0.489 ng/mL. The highest clinical exposure scenario was observed in drug interaction Study BBI-4000-CL-104; when dosed with paroxetine at steady state levels, geometric mean Cmax for sofipirionium was 0.7647 ng/mL. In Thorough QTc Study BBI-4000-CL-106, when 1038 mg sofipirionium was applied topically with occlusion, the geometric mean Cmax for sofipirionium was 2.427 ng/mL. The ratio of the high Cmax achieved in the Thorough QTc study to the Cmax anticipated in a high clinical exposure scenario is 2.427 ng/mL / 0.7647 ng/mL, or 3.2.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	174 mg QD, topical gel	0.487 ng/mL (C _{max,ss})
Sponsor's High clinical exposure scenario	Administration of paroxetine with sofipirionium topical gel	0.7647 ng/mL
Highest dose in QT assessment	1038 mg sofipirionium bromide gel, 15% topically with occlusion	2.427 ng/mL
C_{max} Ratio:	3.2	

Note that on page 42 (of 492) of the study report for Study BBI-4000-CL-102, there is a notable discrepancy in the reported C_{max} values. In Cohort A, the geometric and arithmetic mean C_{max} after 21 days of dosing are 0.487 ng/mL and 2.05 ng/mL, respectively, while the corresponding values in cohort B are 0.489 ng/mL and 0.852 ng/mL respectively. There is apparent inconsistency in arithmetic mean C_{max} values between Cohort A and Cohort B given that participants in Cohort B received a greater dose than Cohort A. This discrepancy in arithmetic mean values appears to be driven by a single outlying subject in cohort A (b) (6) with a C_{max} of 8.59 ng/mL. The geometric mean better reflects central tendency and the analyses in Table 2 are based on the geometric mean.

3.1.2 Nonclinical Safety Pharmacology Assessments

In vitro, sofipirionium bromide exhibited statistically significant potassium ion channel (I_{Kr}) inhibition only at concentrations $\geq 100 \mu\text{M}$ in comparison with vehicle controls in a hERG assay conducted in human embryonic kidney (HEK) 293 cells (Table 2.6.3.4; Study BBI-4000-NC004). The lowest concentration, 10 μM , at which no inhibition was observed, corresponds to 3905 ng/mL based on a molecular weight of 470.4 g/mol for sofipirionium bromide. The in vitro IC₅₀ value for hERG inhibition was estimated to be $>300 \mu\text{M}$, greatly exceeding the human plasma maximum concentration (C_{max}) of approximately 0.03 μM (11.2 ng/mL) sofipirionium following topical dosing of sofipirionium bromide gel, 15% (Study BBI-4000-CL-103).

Reviewer's comment: *The effects of sofipirionium bromide on hERG were evaluated in BBI-400-NC004. The hERG assessment was conducted at near-physiological temperature (i.e., 33 – 35 c) and using a step-ramp voltage protocol (i.e., holding at -80 mV, +20 mV for 1 s and ramp of -0.5 V/s) repeated at 5 s intervals. E-4031 (500 nM) was included at the end to allow for assessment of the contribution of endogenous current and a single-dose of terfenadine (60 nM: 76% inhibition) was included to assess sensitivity. The highest dose (300 uM) resulted in 22.6% inhibition of hERG. Samples were collected at outflow of the perfusion apparatus suggesting limited drug loss (i.e., all measurements were within $\pm 15\%$). These data suggest IC₅₀ is greater than 300 uM (estimated as 965 uM). The free clinical concentration at the highest dose in the thorough QT study: $\sim 3 \text{ nM}$*

(MW: 470.4, PB: 34.8 – 37.8%). The results of the hERG study therefore suggest a low likelihood of direct ion channel block.

In vivo, single iv administration of sofipirionium bromide to telemetered female beagle dogs of up to 1.0 mg/kg were associated with pharmacologically-mediated tachycardia, an expected anticholinergic effect (Table 2.6.3.4; Study BBI-4000-NC-301). Compensatory increases in diastolic pressure were noted at doses ≥ 0.01 mg/kg. There were no sofipirionium 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 sofipirionium bromide was 0.001 mg/kg.

Additional ECG evaluations following topical application of sofipirionium bromide (b) (4) gel, 20% (approximately 76 mg/kg/day) were conducted in a 28-day toxicity study in Sinclair miniature swine and in a 39-week chronic study in Göttingen minipigs (Table 2.6.3.4; Studies BBI-4000-NC-002, NJD0025). There were no sofipirionium bromide related effects on ECG parameters (heart rate, waveform, or RR, PR, QRS, QT, QTc intervals) in either study

Reviewer's comment: The sponsor conducted a single-dose IV study in beagle dogs (n=4) ([BBI-4000-NC-301](#)). The study included four doses (0.001, 0.01 and 0.1 mg/kg and vehicle) during the CV phase and a single dose per animal for the PK phase, which followed the CV phase, with two additional animals from the same colony included for PK at the lowest dose. ECG measurements were summarized in 1-minute bins (0 – 30 min post-dose); 5-minute bins (0.5-to-1-hour post-dose) and 5-minute bins at each hour (2 to 24 h post-dose). QT was corrected for heart rate using Van der Water's correction. Dose-proportional increase in HR were noted with ~20 bpm at 0.01 mg/kg and ~150 bpm at 0.1 mg/kg. No changes in QTc, however, it is unclear if the QT measurements were appropriately corrected for HR. Observed C_{max} in the study was 18.3 and 81.5 ng/mL for 0.01 and 0.1 mg/kg, respectively. C_{max} for the lowest dose (0.001 mg/kg) could not be determined as samples were below the lower limit of quantification (1 ng/mL). The C_{max} for 0.01 and 0.1 mg/kg represent ~8x and ~34x over the highest dose in the thorough QT study based on total drug as protein binding for beagle dogs could not be located.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, Sofipirionium bromide excluded the 10 msec threshold at the supratherapeutic dose level for $\Delta\Delta QTcF$.

Mean $\Delta\Delta QTcF$ ranged from -3.5 ms on the supratherapeutic treatment at 10.5 hours postdose to 3.3 ms on the therapeutic treatment at 1 hour postdose.

Reviewer's comment: Subject (b) (6) included in the sponsor's analysis was excluded due to the incorrect topical dose applied in Period 4. Results from FDA reviewer's analysis are similar to sponsor's results. The largest upper confidence interval bound $\Delta\Delta QTcF$

was below 10 msec for both therapeutic and supratherapeutic dose. Please see Section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

After dosing with 400 mg oral moxifloxacin, a clear increase of mean $\Delta\Delta\text{QTcF}$ was observed with a peak value of 14.5 ms (90% CI: 13.08 to 16.00) at 1 hour postdose.

Reviewer's comment: Results from FDA reviewer's analysis are similar to sponsor's results.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

The sponsor described the categorical analysis in the protocol with the criteria as QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 or >100 beats/min), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline). They did not demonstrate the results of categorical analysis or comment on the outliers in the report.

Reviewer's comment: FDA reviewer's analysis shows no significant outliers for QTc, HR, PR and QRS intervals.

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. The results of the sponsor's analysis show an absence of significant QTc prolongation.

Reviewer's comment: FDA reviewer's analysis was consistent with the sponsor's analysis.

3.2.4 Safety Analysis

There were no deaths or serious AEs in the study. One subject discontinued on day 1 of period 4 due to a mild event of QT prolongation (six days after receiving placebo). The subject (b) (6) had intermittent QTc prolongation (i.e., above 450 msec, but not above 480 msec) throughout the study and was reported to have experienced intraventricular conduction delay. Otherwise, there were no cardiac-related adverse events.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

As described in the sponsor's report, Subject (b) (6) in Period 4 received the Sofpironium bromide gel, 15% in error for approximate 3 minutes instead of the scheduled placebo dose. We excluded this subject in the by-time, categorical and exposure-response analysis.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| < 10$ beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG except for Subject (b) (6). Subject (b) (6) was excluded because of the incorrect topical dose applied in Period 4.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups. The maximum $\Delta\Delta\text{QTcF}$ values by treatment are shown in Table 3.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time-course (unadjusted CIs).

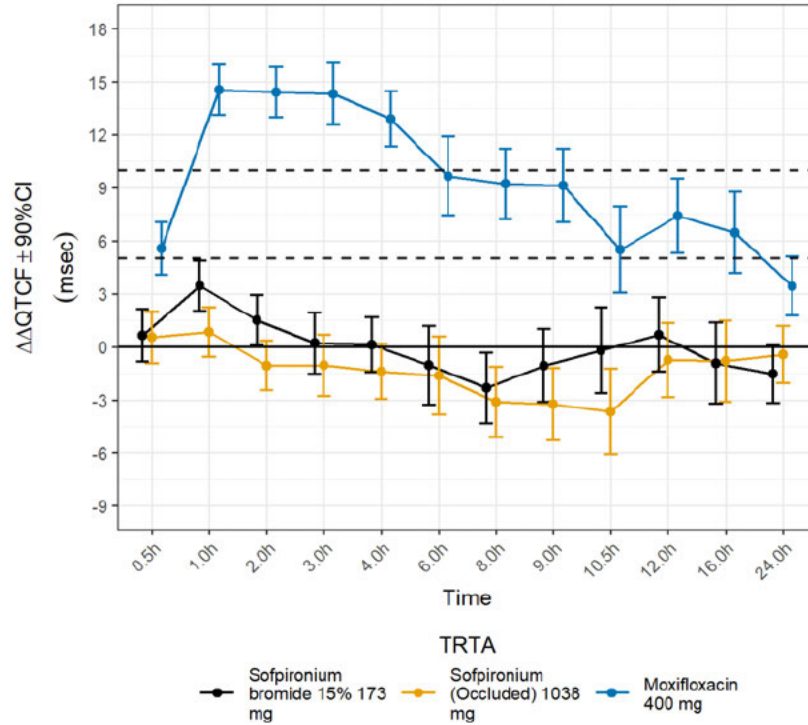


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (Hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Sofpironium bromide 15% 173 mg	58 / 59	1.0	3.5	(2.0 to 4.9)
Sofpironium (Occluded) 1038 mg	59 / 59	1.0	0.8	(-0.6 to 2.2)

4.3.1.1 Assay Sensitivity

The model used for assay sensitivity is the same as that used for the primary model. The time-course of changes in $\Delta\Delta\text{QTcF}$ is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4).

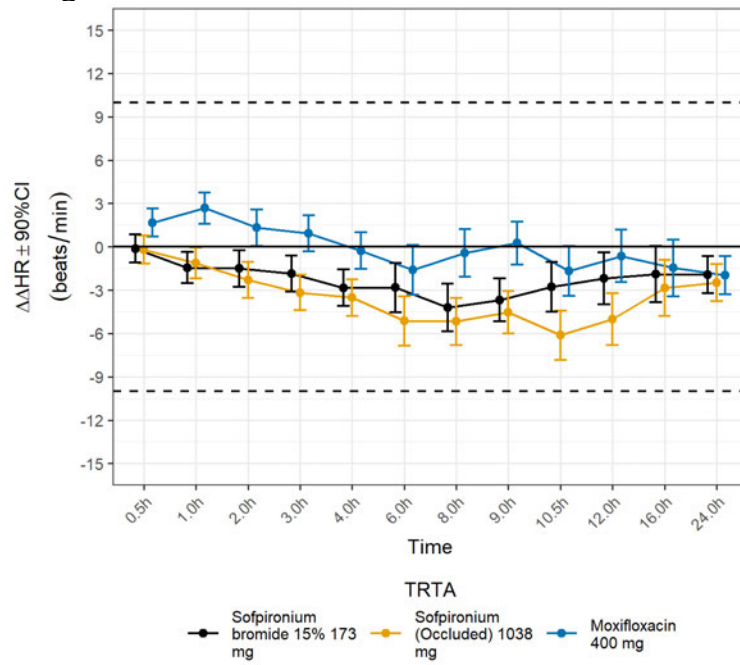
Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (Hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	57 / 59	1.0	14.5	(13.1 to 16.0)	(12.6 to 16.5)

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for different treatment groups.

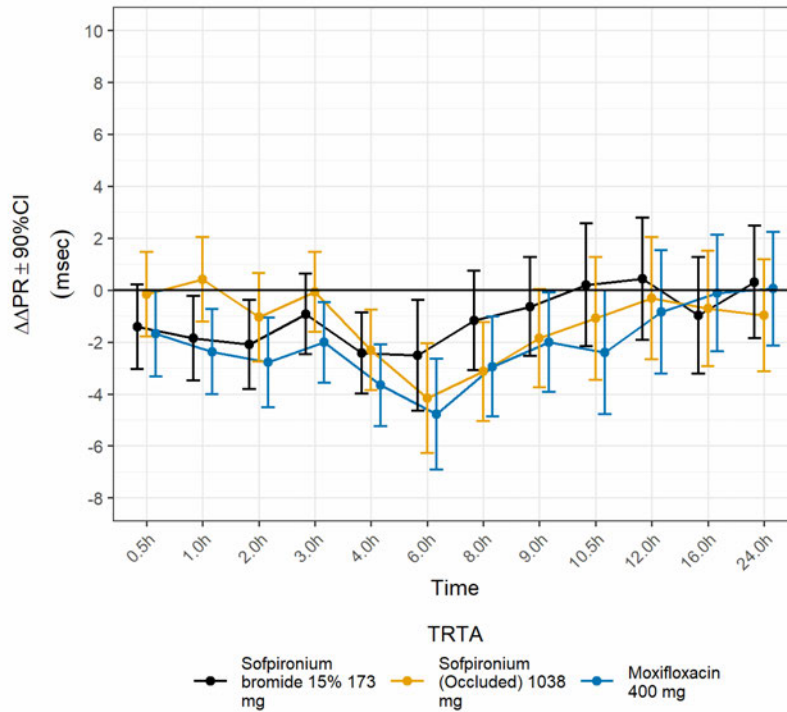
Figure 2: Mean and 90% CI of $\Delta\Delta\text{HR}$ Time-course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ for different treatment groups.

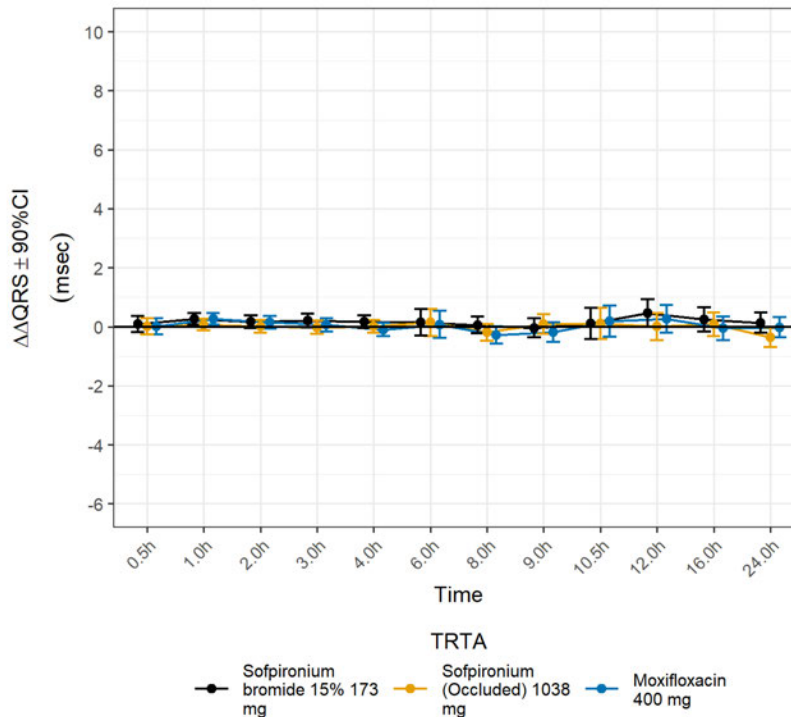
Figure 3: Mean and 90% CI of $\Delta\Delta\text{PR}$ Time-course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta\text{QRS}$ for different treatment groups.

Figure 4: Mean and 90% CI of $\Delta\Delta\text{QRS}$ Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects had QTcF value >500 msec. None of the subjects had ΔQTcF value >30 msec.

4.4.2 HR

None of the subjects treated with sofipironium had HR>100 beats/min.

4.4.3 PR

None of the subjects had PR value >220 msec and 25% over baseline.

4.4.4 QRS

None of the subjects had QRS value >120 msec and 25% over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

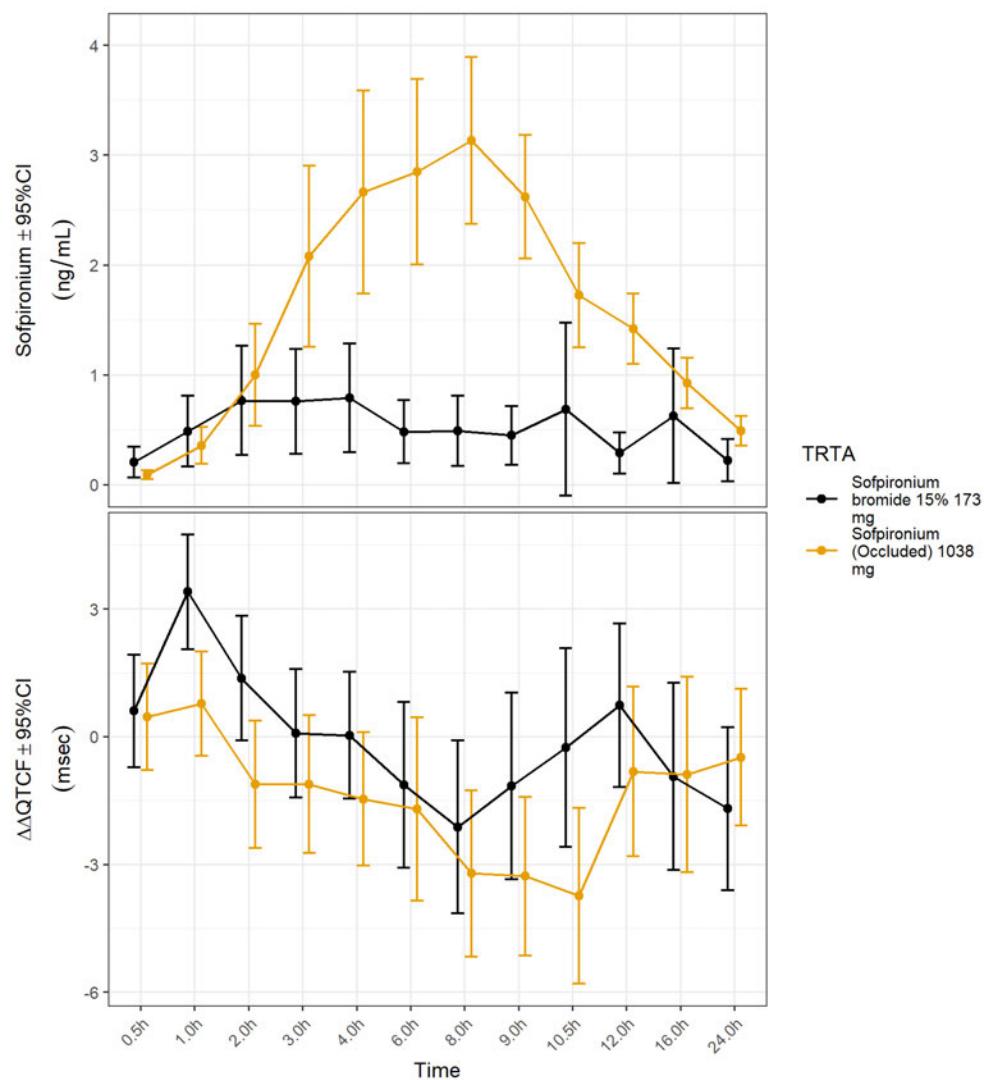
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK, except for Subject (b) (6) who was excluded because of the incorrect topical dose applied in Period 4.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and $\Delta\Delta\text{QTcF}$; and 3) absence of a nonlinear relationship.

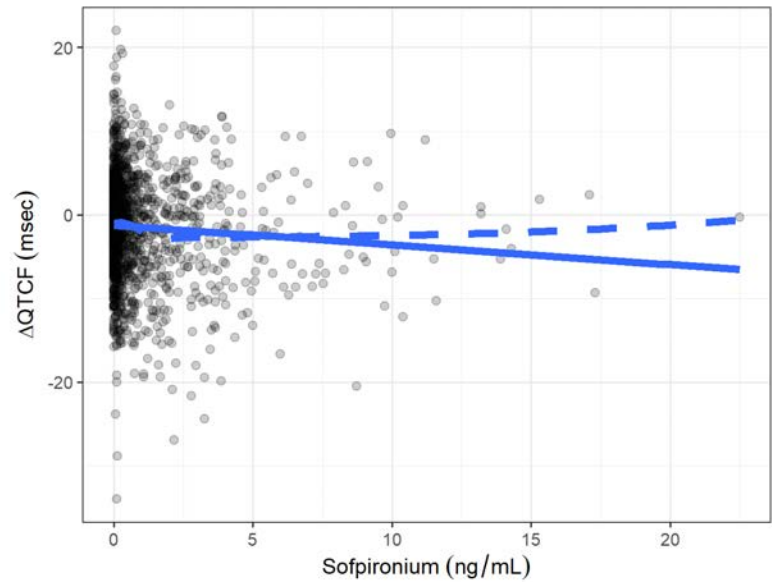
Figure 2 shows the time-course of $\Delta\Delta\text{HR}$, with an absence of significant $\Delta\Delta\text{HR}$ changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and $\Delta\Delta\text{QTcF}$, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF , and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)¹



¹ $\Delta\Delta\text{QTcF}$ shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 5Table 55.

Figure 7: Goodness-of-fit Plot for QTcF

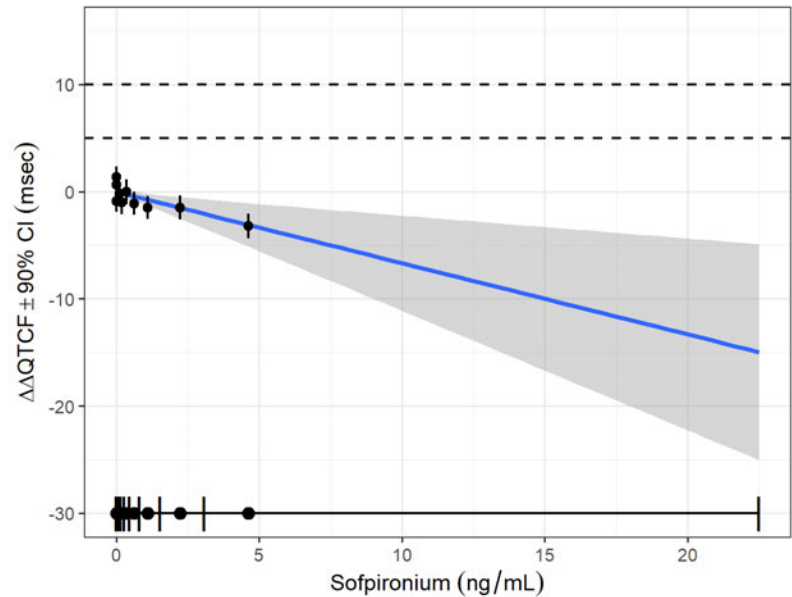


Table 55: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Sofpironium (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Sofpironium bromide 15% 173 mg	1	0.4	-0.3	(-0.8 to 0.1)
Sofpironium (Occluded) 1038 mg	1	2.6	-1.7	(-2.9 to -0.6)

4.5.1.1 Assay Sensitivity

Assay sensitivity was established using by-time analysis. Please see section 4.3.1.1 for additional details.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

APPEARS THIS WAY ON ORIGINAL

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

Protocol previous reviewed under IND 121256 (DARRTS [11/27/2018](#)).

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