CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217347Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 121256

MEETING MINUTES

Brickell Biotech, Inc.
Attention: Michael P. Doyle, PhD
Vice President, Global Regulatory Affairs
5777 Central Avenue, Suite 102
Boulder, CO 80301

Dear Dr. Doyle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofpironium bromide.

We also refer to the teleconference between representatives of your firm and the FDA on January 12, 2022. The purpose of the meeting was to discuss the sofpironium bromide gel development program and a planned New Drug Application.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Craig Johnson, Regulatory Project Manager at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 12, 2022, 10:30am – 11:30am EST
Meeting Location:	Teleconference
Application Number:	IND 121256
Product Name:	sofpironium bromide
Proposed Indication:	topical treatment of primary axillary hyperhidrosis in adults and children aged 9 years and older.
Sponsor Name:	Brickell Biotech
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Shari L. Targum, MD, MPH, FACP, FACC
Meeting Recorder:	Craig Johnson PharmD

FDA ATTENDEES

Shari L. Targum, MD, MPH, FACP, FACC, Deputy Director, Division of Dermatology and Dentistry (DDD)

David Kettl, MD, FAAP, Clinical Team Leader, DDD

Roselyn E. Epps, MD, Clinical Reviewer, DDD

Shlomit Halachmi MD, PhD, Clinical Reviewer, DDD

Selena Daniels, PharmD, MS, Team Leader, Division of Clinical Outcome Assessment (DCOA)

Yasmin Choudhry, MD, Reviewer, COA

Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics (DB) III

Marilena Flouri, PhD, Biometrics Reviewer, DB III

Lili Garrard, PhD, Patient-focused Statistical Support (PFSS) Team Leader, DB III

Marian Strazzeri, MS, PFSS Reviewer, DB III

Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)

Da Zhang, PhD, Clinical Pharmacology Reviewer, DIIP

Catherine Gilbert, Quality Microbiology Reviewer, Division of Microbiology Assessment II/Branch IV

Hong Cai, PhD, Chemist, Office of Product Quality, Office of New Drugs

Jane Chang, PhD, Product Quality Assessor

Khalid M. Khan, MS, RPh, Chemist, Office of Pharmaceutical Manufacturing Assessment (OPMA), Division of Process and Manufacturing IV

Craig Johnson PharmD, Regulatory Health Project Manager, Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)

1.0 BACKGROUND

The purpose of this meeting is to discuss the sofpironium bromide gel development program and a planned New Drug Application.

FDA sent Preliminary Comments to Brickell Biotech on January 10, 2022.

2.1. Chemistry, Manufacturing, and Controls (CMC)

Question 1:
Does FDA agree that the CMC information to be provided in the NDA is sufficient to support its filing and review?

FDA Response to Question 1:
It is acceptable in the NDA to reference the details of the drug substance manufacturing processes and controls to the (b) (4) Include in the NDA, at minimum, data that demonstrates an understanding of the Active Pharmaceutical Ingredient (API) general properties, impurity profile, current specification, and suitability of the analytical methods. Additionally, include API batch release data for the drug product registration batches. Reference data that demonstrates an understanding of the API stability profile to support a retest date.

From the drug product perspective, the CMC information described in the meeting package is not sufficient to support filing and review. Include the following in your NDA submission:

a) Provide extractable/leachable data for the product contact materials of the proposed commercial container closure system

b) Regarding the drug product specification:
   a. Include delivered-dose uniformity in the drug product stability specification.
   b. Include (b) (4) for determination of total degradation products for both release and stability specifications.
   c. Revise the acceptance criterion for minimum fill from (b) (4)

c) In the drug product composition (Table 6), the function of citric acid is listed as [redacted] However, in section 11.2.3.3, you state, [redacted] Update the function of citric acid in 3.2.P.1.

d) Perform a risk assessment for elemental impurities per ICH Q3D(R2) Draft Guideline (https://www.ich.org/page/quality-guidelines).

e) Perform a risk assessment for [redacted] impurities. Where appropriate, testing and acceptance criteria of [redacted] impurities may be required for the drug product specification. See FDA guidance entitled [redacted] for details.

f) Perform a risk assessment and/or establish a control strategy [redacted]

g) Include data to support your statement [redacted]

Adequacy of information, e.g., acceptance criteria of critical quality attributes, will be determined during the NDA review.

Additional CMC information is also required regarding microbiology. Submit method suitability testing results that support the microbial limits tests proposed in the release and stability specifications. [redacted]

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Question 2:
Does the Agency agree with the development plan for the new (b) (4) analytical method and the proposed specification?

FDA Response to Question 2:
See *FDA response to Question 1*. The development plan for the new (b) (4) analytical method appears reasonable.

Your plan to qualify the (b) (4) in your ongoing 4-week repeat-dose toxicity study in mice appears reasonable from a nonclinical perspective. However, the final determination of the data adequacy and proposed acceptance criterion will be a review issue.

2.2. Nonclinical

Question 3:
Does FDA agree that the completed nonclinical studies satisfy all requirements to support filing and review of an NDA for sofpironium bromide gel?

FDA Response to Question 3:
We acknowledge that your nonclinical package includes safety pharmacology assessment, a 26-week subcutaneous study in rats, a 39-week dermal study in minipigs, an ICH battery of genotoxicity studies, a subcutaneous carcinogenicity study in rats, a dermal carcinogenicity study in mice, a subcutaneous fertility study in rats, subcutaneous embryofetal development studies in rats and rabbits, a pre- and postnatal development study in rats, and a subcutaneous juvenile animal toxicity study in rats to support the safety of your topical drug product. In addition, you have assessed the ocular irritation potential, sensitization potential, and phototoxicity potential of your topical drug product.

Your proposed nonclinical development program appears reasonable to support an NDA submission. The final determination of the data adequacy to support your NDA application will be made after review of all the submitted nonclinical information.

To enable us to conduct the statistical review of the dermal mouse carcinogenicity study and the subcutaneous rat carcinogenicity study, submit the SAS tumor data sets (tumor.xpt) for each carcinogenicity study to your NDA. Follow the attached standard format for preparing the data.

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Typ**	**Codes**	**Comments**
STUDYNUM	Study number	char		3
ANIMLNUM	Animal number	char		1,3
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		3,4
TUMORNAM	Tumor name	char		3,4
ORGANCOD	Organ/tissue code	char		3,5
ORGANNAM	Organ/tissue name	char		3,5
DETECTTM	Time in days of detection of	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	4
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	4
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD
when the organ is unusable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

2.3. Clinical

Question 4:
Pending the Agency's filing review of the NDA, are the efficacy data from the two adequate and well-controlled Phase 3 studies (BBI-4000-CL-301 and BBI-4000-CL-302) adequate to support the submission of an NDA and allow the Agency to evaluate the effectiveness of sofpironium bromide gel, 15%, in the treatment of primary axillary hyperhidrosis?

FDA Response to Question 4:
Yes.

Question 5:
Does the Agency agree that the extent of population exposure to be included in the proposed safety database will be acceptable for the Agency to evaluate the safety of sofpironium bromide for the proposed indication?

FDA Response to Question 5:
Your meeting package information indicates that numbers for subjects exposed to multiple doses of study drug at any concentration are 1587 total and 418 for at least 6 months. For subjects exposed to study gel 15%, commercial preparation the totals are 879 exposed, 735 multiple dose exposure, 222 exposed for ≥ 6 months, and 118 subjects exposed for ≥ 48 weeks.

It appears that your proposed database meets the minimal standards for a safety review of your application. The final determination of the adequacy of your safety assessments to support your product safety in your NDA application will be made after review of all the submitted information.

Question 6:
Does the Agency agree with the proposed pooling strategy and inclusion of selected clinical data for the ISS and ISE, and that no additional study pools are needed to support the NDA for the proposed indication?

FDA Response to Question 6:
Your plan to provide an Integrated summary of Efficacy (ISE) by pooling the phase 3 trials (BBI-4000-CL-301 and BBI-4000-CL-302) appears reasonable. The ISE should include discussions regarding the strength of evidence across all trials, including

discussion of any difference in outcomes across trials. Higher response rates for HDSM-Ax-7 are observed in Trial BBI-4000-CL-302 than BBI-4000-CL-301 and the vehicle response rate in Trial 302 is similar to the active in the Trial 301.Explore whether there are potential sources for such variability in terms of the patient characteristics and/or the conduct of the trial because this may shed light on interpreting study findings.

You propose 4 pooling groups for the safety analyses with different objectives. For a safety profile comparison between the to-be marketed formulation in the US (i.e., IPM1) at 15% concentration and the vehicle, the phase 3 trials could be pooled along with the phase 2 trial BBI-4000-CL-203 (pool only sofpironium bromide gel, 15%, and vehicle arms). The phase 3 trials and the phase 2 trial BBI-4000-CL-203 are of similar design [same trial duration, similar study population (adults in phase 2 and at least 9 years old in phase 3), same formulation]. Therefore, pooling the phase 2 trial along with the phase 3 trials can provide additional precision to the safety analyses. Such a pool could be additional to the ones already proposed in your ISS.

Pooling groups 2-4 are exploratory because they pool data from trials of different population, different design, and different formulations.

Meeting Discussion:
The sponsor stated that they plan to update their Analysis Group 2 for the Integrated Summary of Safety (ISS) per the Agency's recommendation to include the two pivotal phase 3 trials (BBI-4000-CL-301 and BBI-4000-CL-302) and the phase 2 trial BBI-4000-CL-203. The sponsor inquired about conducting subgroup analyses based on Analysis Group 1, comprising the two pivotal phase 3 trials only, since the phase 2 trial does not include pediatric subjects. The FDA recommended performing the subgroup analysis based on the larger analysis group (i.e., the phase 3 trials and the phase 2 trial BBI-4000-CL-203) because subgroups tend to have limited number of subjects and a larger pool is more likely to capture differential safety signals across subgroups.

Question 7:
Does the Agency agree with the proposal to place the full ISE text portion of the NDA in Module 2 (Section 2.7.3) and the ISE tables, figures, and datasets in Module 5 (Section 5.3.5.3)?

FDA Response to Question 7:
If Module 2.7.3 would be sufficiently detailed to serve as the summary portion of the ISE, your proposal to provide the text portion of the ISE in Module 2.7.3 and the tables, figures, and datasets in Module 5.3.5.3 in accordance with the guidance for industry, Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document appears reasonable.

Question 8:
Does the Agency agree that the SAS programming code to support reproduction of datasets and analyses will be provided for only the pivotal Phase 3 studies (BBI-4000-CL-301 and BBI-4000-CL-302)?

FDA Response to Question 8:
We agree with your proposal to provide the SAS code needed to support re-creation of all ADaM datasets and the SAS code necessary to reproduce the analysis of co-primary, secondary, other supportive efficacy endpoints and the sensitivity analyses of the primary endpoint. Include the SAS programming code for all tipping analyses as well.

We also have the following general comments regarding analysis datasets:

a. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

b. The analysis dataset documentation (Define.xml) should include adequate detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. Submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, submit study protocols including the statistical analysis plan (SAP), all protocol and SAP amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Additional biostatistics comment:
The SAPs submitted on August 13, 2021 specified that the estimand for the co-primary efficacy endpoints is the difference in proportions between sofpironium bromide gel and vehicle. However, Table 17 of the meeting package only presents odds ratios. Results based on the estimand of the difference in proportions between sofpironium bromide gel and vehicle should be presented because it is easier to interpret for labeling purpose.

Additional COA comment:
Submit the following for studies BBI-4000-CL-301 (CARDIGAN I) and BBI-4000-CL-302 (CARDIGAN II) under Section 5.3.5.3 of the eCTD[1]:

[1] Per the *FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009; accessible at: https://www.fda.gov/regulatory-

a) exact copies (e.g., screenshots) of both the “original” and “child” versions of the full HDSM-Ax as administered

b) a final psychometric analysis plan

c) a COA Evidence Dossier compiling and synthesizing all psychometric and meaningful change results

d) all datasets and statistical program code used to conduct all psychometric analyses described in the psychometric analysis plan and otherwise conducted using HDSM-Ax and GSP scores from patients enrolled, along with all corresponding dataset reviewer guides, define files, and annotated electronic case report forms (CRFs).

Post Meeting Comments:
We would like to clarify that the COA Evidence Dossier requested in FDA additional COA comment (c) should include a compilation and synthesis of *all qualitative and quantitative psychometric analyses*, including those conducted to evaluate meaningful within-patient change.

Question 9:
Does the Agency agree with the BIMO proposal to include the two pivotal Phase 3 studies (BBI-4000-CL-301 and BBI-4000-CL-302) in the summary-level clinical site dataset?

FDA Response to Question 9:
Yes. We anticipate that the clinical trial inspections sites will come from those sites that participated in the phase 3 trials.

Technical questions that cannot be addressed in the guidance, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, can be addressed directly to ESUB@fda.hhs.gov as outlined in the guidance.

Question 10:
Does the Agency agree with the adequacy of the Phase 3 psychometric analysis plan to demonstrate that the scores produced by the HDSM-Ax-7 in Studies BBI-4000-CL-301 and BBI-4000-CL-302 are reliable, valid, interpretable, and therefore sufficiently trustworthy to support product approval and labeling decisions?

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information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims).

FDA Response to Question 10:

Ideally, there should have been agreement on the psychometric analysis plan (specifying the quantitative evaluation of measurement properties and meaningful change) prior to data unblinding. The adequacy of the data generated from these analyses will be a review issue. We have the following comments on your psychometric analysis plan and statistical analysis plans for CARDIGAN I and II.

1. You indicate that HDSM-Ax Adult and Child version scores will be pooled for the psychometric analyses. We do not agree with this approach because some of the items differ between the two instruments and measure different concepts (e.g., Items 2a and 2c). Psychometrically evaluate these instruments separately because they are different instruments.

2. You indicate that the defined psychometric analysis population will include BBI-4000-CL-301 (and -302) ITT patients (b) (4) Conduct the psychometric analyses for participants with complete data for each of the seven items of the HDSM-Ax-7.

3. We note your plan to provide descriptive statistics including ceiling and floor effects for the HDSM-Ax-7. The following item analyses should also be conducted:

   a. The number and percentage of missing responses for each item at each measurement time point.

   b. For items using an ordinal response scale, provide the number and percentage of patients endorsing each response category with corresponding histograms.

   c. The measure of correlation used should be appropriate for the types of data being analyzed.

4. We advise against (b) (4)

5. For assessment of known-groups validity, in addition to determining known groups based on the response categories for Patient Global Impression of Severity (PGI-S) (i.e., none, mild, moderate, and severe, very severe), also use

HDSM-Ax item 6 because the recall period more closely aligns with the target COA endpoint.

6. For the sensitivity to change analysis (responsiveness), create “improved,” “no change,” and “worsened” anchor groups based on changes in score for both the PGIS scale and HDSM-Ax item 6 from baseline (i.e., 1-point improvement, 2-point improvement, 3-point improvement, 4-point improvement, no change, 1-point worsening, 2-point worsening, 3-point worsening, 4-point worsening) separately. Similarly perform this analysis based on each response category achieved in the Patient Global Impression of Change (PGIC) scale, separately (as opposed to collapsed response categories).

7. HDSM-Ax Item 6 has limitations as an external anchor. Specifically, the recall period is not consistent with the assessment time period of the prespecified endpoint (i.e., the recall period of Item 6 is “the past week” whereas the recall period of the target COA endpoint is “since you woke up yesterday”). Therefore, it will be difficult to interpret the data generated from its corresponding anchor-based analyses.

8. Distribution-based methods (e.g., effect sizes, certain proportions of the standard deviation and/or standard error of measurement) are only supportive to anchor-based methods.

9. In addition to the anchor-based empirical cumulative distribution function (CDF) and the probability density function (ePDF) curves, submit a supportive graph (i.e., eCDF) of within-patient changes in scores from baseline with separate curves for each treatment arm (i.e., treatment vs. placebo). The graph will be used to assess whether the treatment effect occurs in the range that patients consider to be clinically meaningful.

Additional Comments

10. The copy of the HDSM-Ax (adult and child versions) in Appendix 3 of the meeting package differs from the copies included in the protocols for Studies BBI-4000-CL-301 and BBI-4000-CL-302 and the psychometric analysis plan. Clarify which versions of the HDSM-Ax (adult and child versions) were administered in Studies BBI-4000-CL-301 and BBI-4000-CL-302.

11. In the HDSM-Ax (adult and child versions included in the protocols for Studies BBI-4000-CL-301 and BBI-4000-CL-302), there is a footnote that states “These HDSM-Ax questions can appear slightly different when administered in an electronic format.” In your NDA submission, submit exact copies of the HDSM-Ax as it was administered in Studies BBI-4000-CL-301 and BBI-4000-CL-302 (including both copies of paper version and electronic screen shots) and any associated training materials and user manuals.

Meeting Discussion:
The sponsor stated that scores from the adult version (for patients aged ≥12 years) and child version (for patients < 12 years of age) of the HDSM-Ax were pooled in the CARDIGAN I and II efficacy analyses and will, likewise, be pooled in the planned psychometric analyses as there are 5 participants who completed the HDSM-Ax child version across CARDIGAN I and II combined. FDA continued to recommend not pooling scores from the adult and child versions of the HDSM-Ax as these are distinct measures of different concepts (e.g., differences between versions in items 2a and 2c) that yield scores on different response latent scales. Further, no qualitative or quantitative evidence has been submitted to support pooling scores on these two measures. FDA recommended conducting psychometric analyses using only scores on the HDSM-Ax adult version. The sponsor indicated they have qualitative data to support the equivalence of scores on the adult and child versions of the HDSM-Ax. FDA recommended that the sponsor submit these qualitative data in their NDA submission and noted that pooling scores on these two measures will be a review issue. FDA additionally noted that the handling of missing HDSM-Ax-7 item responses in the scoring algorithm, efficacy analyses, and psychometric analyses in CARDIGAN I and II will also be a review issue.

The FDA clarified that the sponsor should use HDSM-Ax item 5 for assessment of known-groups validity, in addition to the Patient Global Impression of Severity. The sponsor noted that they plan to also use HDSM-Ax item 5 as an external anchor for their anchor-based analyses.

The FDA clarified that the anchor groups suggested for the sensitivity to change analysis (responsiveness) would also apply to the anchor groups used for the anchor-based analyses.

The sponsor clarified that the psychometric analysis population specified in Psychometric Analysis Plan Section 3.3 includes CARDIGAN I and II patients in the intent-to-treat (ITT) population with complete HDSM-Ax-7 response data.

The FDA recommended that the sponsor also conduct the dimensionality analyses proposed in Psychometric Analysis Plan Section 4.4.3 using HDSM-Ax responses collected prior to treatment initiation at baseline (Visit 4 / Study Day 1). The sponsor agreed.

The FDA stated it would provide additional feedback on the Psychometric Analysis Plan as post-meeting comments.

Post Meeting Comments:
We have the following additional comments on your current Psychometric Analysis Plan:

1. The proposed threshold of [redacted] for the "corrected" item-total correlations analysis proposed in Psychometric Analysis Plan Section 4.4.3.1 is too low. Given the overlap in item content and that all HDSM-Ax-7 items are intended to measure the same overarching construct, a more appropriate threshold would be at least 0.7. Please revise the Psychometric Analysis Plan accordingly.

2. Regarding your proposed anchor-based analyses, we have the following comments:

   a. We do not agree with [redacted]

   b. For HDSM-Ax items 4, 5, 6, and 7, specify a focal anchor change score for developing a threshold for meaningful within-patient change.

   c. Psychometric Analysis Plan Section 4.5.1 states: [redacted] It may be challenging to characterize [redacted]

   d. Psychometric Analysis Plan Section 4.5.1 states: [redacted] Clarify why it would not be possible [redacted]

2.4. Clinical Pharmacology

Question 11:
Brickell has conducted eight studies to assess the PK of the proposed to-be-marketed formulation for sofpironium bromide gel, 15%, and three additional PK studies to support formulation changes. Brickell believes that the clinical pharmacology studies are sufficient to support the submission of the NDA, and that no further studies are necessary for the Division's review of the clinical pharmacology portion of the NDA.

Does the Agency agree?

FDA Response to Question 11:
You have assessed PK of sofpironium and/or the primary metabolite BBI-4010 across three formulations, including eight studies utilizing the to-be-marketed IPM1

formulation. You've also conducted a maximum use PK study in adults and pediatric subjects, drug-drug interaction, and QT studies. The clinical pharmacology studies conducted appear reasonable to support filing of your NDA. However, the relevance and adequacy of your study data to support your NDA application will be determined at the time of NDA review.

In your NDA, submit the bioanalytical method validation and bioanalysis reports as well as information to support long-term storage stability of your PK samples and incurred sample re-analysis for review.

Question 12:
Does the Agency agree that the analyses outlined in the Sofpironium Bromide Gel Modeling and Simulation Analysis Plan to characterize potential sofpironium systemic exposures and exposure-safety relationships, are sufficient to support approval of sofpironium bromide gel, 15% in patients with primary axillary hyperhidrosis?

FDA Response to Question 12:
Your proposed modeling and simulation analysis plan, namely developing a population PK model to identify covariates impact on the systemic exposure of sofpironium as well as utilizing the developed population PK model to derive safety exposure-response relationship appears reasonable. The feasibility, adequacy and applicability of your model(s) will be determined at the time of NDA review.

2.5. Regulatory

Question 13:
Does FDA agree that a REMS will not be required and that the IFU evaluated in human factors studies can be used in lieu of a Medication Guide?

FDA Response to Question 13:
Based on the information presented in the meeting package, it appears unlikely that a REMS will be required for your program.

Assessment of safety, your proposed instructions for use (IFU), and the need for risk evaluation and mitigation strategies (REMS) will occur during the review cycle. If a safety issue is identified requiring a REMS, we will work closely with you to develop a plan to ensure safe use.

Likewise, we cannot determine the need for a Medication Guide until the safety experience from your development program is reviewed.

FDA requires that Medication Guides be issued with certain prescribed drugs and biological products when the FDA determines that:

a. certain information is necessary to prevent serious adverse effects

b. patient decision-making should be informed by information about a known serious side effect with a product, or

c. patient adherence to directions for the use of a product are essential to its effectiveness.

Further discussion on these issues is provided in the FDA guidance, *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*.

3.0 ADMINISTRATIVE LANGUAGE

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable,

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the meeting package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of

the cover letter for the Type C meeting request.

4.0 ATTACHMENTS AND HANDOUTS

- Brickell Biotech response to Preliminary Comments

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/

SHARI L TARGUM
02/07/2022 11:04:13 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121256

MEETING MINUTES

Brickell Biotech, Inc.
Attention: Deepak Chadha, MS, MBA, RAC
Chief Regulatory, Preclinical & Quality Compliance Officer
5777 Central Avenue, Suite 102
Boulder, CO 80301

Dear Mr. Chadha:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofpironium bromide gel, 15%.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2018. The purpose of the meeting was to discuss the development program for sofpironium bromide gel, 15%.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: February 7, 2018 at 9 am
Meeting Location: WO22, Rm. 1313

Application Number: IND 121256
Product Name: sofpironium bromide gel, 15%
Proposed Indication: for the topical treatment of severe primary axillary hyperhidrosis.
Sponsor Name: Brickell Biotech, Inc.

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products
David Kettl, MD, FAAP, Clinical Team Leader, DDDP
Roselyn E. Epps, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Cindy (Xinguang) Li, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III
Marilena Flouri, PhD, Biostatistics Reviewer, DB III
Selena Daniels, PharmD, MS, Team Leader, Clinical Outcomes Assessment (COA)
Michelle Campbell, PharmD, Reviewer, COA
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Yichun Sun, PhD, Acting Quality Assessment Lead, DNDP II, NDPB V
Mishale Mistry, PharmD, MPH, Team Leader, OSE/DMEPA
Madhuri Patel, PharmD, Safety Evaluator, OSE/DMEPA
Bob Pratt, PharmD, Reviewer, DRISK
John McMichael, Team Leader, CDRH
Sapana Patel, PharmD, Pharmacist and Lead Reviewer, CDRH
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Patricia Walker, MD, PhD, President and Chief Scientific Officer
Deepak Chadha, MS, MBA, RAC, Chief Regulatory, Preclinical & Quality Compliance Officer

Larry Romel, Senior Vice President, Clinical Operations
Herbert Brinkman, PhD, Vice President, CMC
Michael Doyle, PhD, Vice President, Global Regulatory Affairs
Aron Aizenstat, PMP, Sr. Project Manager
(b) (4)

1.0 BACKGROUND

Purpose of Meeting:
The purpose of this meeting is to discuss the development program for sofpironium bromide gel, 15%

Regulatory Correspondence History:

We have had the following meeting:

- March 5, 2014: Pre-IND Meeting

We have sent the following correspondences:

- December 14, 2017: Advice/Information Request
- October 17, 2017: Advice/Information Request
- September 14, 2017: Advice/Information Request
- June 14, 2017: Advice Letter
- January 5, 2017: Advice/Information Request
- September 13, 2016: Advice/Information Request
- May 27, 2016: Advice Letter
- January 6, 2016: Advice Letter
- March 27, 2015: Advice Letter
- February 24, 2015: Study May Proceed Letter

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls (CMC)

Question 1:
Does FDA agree that the synthetic process, GMP starting materials, manufacturing controls, and plans for registration batches are adequate to support an NDA?

FDA Response to Question 1:
(b) (4)

The critical steps (b) (4) for the process are reasonable for this stage of development. However, when you file your NDA these will need to be defined.

The designation of (b) (4) as starting materials appears reasonable if they comply with the approaches as outlined in ICH Q11. We remind you that a final determination will be made at the time of NDA review. Refer to the following ICH Guidance's for information on development and manufacture of drug substances.

- Guidance for Industry: ICH Q11: Development and Manufacture of Drug Substances https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf

- Draft Guidance for Industry: ICH Q11 Development and Manufacture of Drug Substances : Questions and Answers (regarding the selection and justification of starting materials) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM542176.pdf

We agree that the four batches (b) (4) can be used as the registration batches for the NDA. At least 12 months of long term stability data and 6 months of accelerated stability data should be available for review on a minimum of three batches at the time of the NDA submission.

Question 2:
Does FDA agree that the proposed specifications, stability data, and stability commitment for the drug substance are acceptable to support the proposed Phase 3 clinical studies and an NDA?

FDA Response to Question 2:
We agree that the tests in your proposed specifications are reasonable for both Phase 3 studies and the NDA. The decision on the final acceptance criteria is a NDA review issue. We remind you that any impurities above the ICH Q3A(R2) levels would need to be adequately qualified and/or justified. The stability protocols and commitments are reasonable.

Question 3:
Does FDA agree that the manufacturing process and controls, product specifications, plans for three registration batches, and stability plans are adequate to support an NDA?

FDA Response to Question 3:
We agree in principle regarding your drug product manufacturing process. (b) (4)

The acceptance criteria of all the tests in your drug product specification should be set before initiating Phase 3 clinical studies.

Your proposed registration stability studies with 3 pilot scale batches of the drug product appear reasonable to support NDA submission. The expiration dating period of the drug product will be determined based on available stability data during NDA review.

Question 4:
Does FDA agree that the plan to identify and qualify drug product degradants is adequate?

FDA Response to Question 4:
Your proposed identification plan for degradation products of the API in the drug products appears reasonable.

Your proposed qualification plan for identified degradation products above the ICH threshold appears reasonable.

Additional CMC Comments

- The strengths of the drug products should be expressed based on the active moiety of the drug, the free base (sofpironium), per guidance for industry *Naming of Drug Products Containing Salt Drug Substances*.
- Results of in-use stability study on stability samples from representative time points of long-term stability study should be provided in your NDA submission.
- Results of temperature cycle stress studies on the drug product should be provided in your NDA submission.
- Results of extractable and leachable studies on the container closure system should be provided in your NDA submission.
- Results of photostability study should be included in your NDA submission.

Meeting Discussion:
The sponsor inquired about the duration of the in-use stability study. The Agency stated that only stability samples of representative timepoints from a long-term stability study need to be tested for the in-use stability study. The in-use stability tests should be conducted on the representative long-term stability samples at several timepoints during the period of simulated use of the product.

2.2. Nonclinical

Question 5:
Does FDA agree that the set of completed and proposed nonclinical studies is sufficient to support an NDA submission, and, assuming no unexpected or untoward findings in planned or ongoing studies, that no additional nonclinical studies will be required?

FDA Response to Question 5:
Your nonclinical package appears reasonable to support an NDA submission. However, the available nonclinical data do not support the safety of subjects 9 years to less than 12 years of age. A juvenile animal study should be conducted with your drug product to support the safety of subjects 9 years to less than 12 years of age in clinical trials. If you intend to resubmit your waiver request for conduct of juvenile animal toxicity studies, then you will need to submit the full study report for the clinical maximal use pharmacokinetics study that demonstrates negligible systemic absorption under maximal clinical use conditions to support your waiver request (refer to our Advice Letter dated December 14, 2017).

2.3. Clinical/Clinical Pharmacology/Biostatistics

Introductory Comments

You propose to conduct BBI-4000-CL-301 and BBI-4000-CL-302**,** two identical, multicenter, randomized, double-blind, vehicle-controlled Phase 3 studies for development of your product.

In each study, approximately 660 subjects age ≥ 9 years with axillary hyperhidrosis at approximately 50 clinical sites will be randomized to receive 5% sofpironium bromide gel, or 15% sofpironium bromide gel, or vehicle gel (placebo) in a 1:1:1 ratio. Subjects will apply the investigational product once daily at bedtime, to both axilla for 42 consecutive days.

The proposed study endpoints:

Primary endpoint:

- The proportion of subjects achieving at least a (b) (4)-point improvement in the hyperhidrosis disease severity measure (HDSM-Ax) score and (b) (4) reduction in gravimetrically measured sweat production (GSP) from baseline to end of therapy.

Secondary endpoints:

- The proportion of subjects achieving at least a (b) (4)-point improvement in HDSM-Ax from baseline.

(b) (4)

- The proportion of subjects achieving at least a 50% improvement in gravimetrically measured sweat production from baseline.

Other proposed endpoint:

(b) (4)

Gravimetric assessments and patient-reported outcomes HDSM-Ax, HidroQoL and DLQI will be recorded during the study at predefined time points. Vital signs, local tolerability assessments (including burning, itching, dryness, scaling and erythema assessed using standardized scales), and adverse events will be collected at each visit.

You also propose to conduct BBI-4000-CL-303, a long-term safety study. Subjects who have completed 48 weeks of dosing and 52 weeks of clinical assessments will be eligible to enroll in the long-term, open label Phase 3 study for safety. A maximum of 300 subjects, at approximately 30 clinical sites, will be randomized to receive either 5% or 15% sofpironium bromide gel in a 1:2 ratio, respectively, to achieve enrollment of approximately 150 subjects (100 subjects dosed with 15% gel and 50 subjects dosed with 5% gel). Subjects will apply the investigational product once daily at bedtime, to both axillae for 48 weeks.

Patient-reported outcomes: HDSM-Ax, DLQI, and HidroQoL will be recorded during the study at predefined time points. Vital signs, local tolerability assessments (including burning, itching, dryness, scaling and erythema assessed using standardized scales), and adverse events will be collected at each visit. Blood and urine samples will be collected and analyzed at the Screening Visit and at the End of Therapy Visit for routine hematology, chemistry, and urinalysis parameters, and urine pregnancy tests (UPT) for FOCBP will be taken throughout the course of the study.

Two Patient Global Impression Scales will be administered as additional anchors and to confirm the threshold for meaningful change. These include the Patient Global Impression of Severity (PGI-S) to be administered with each administration of the HDSM-Ax and the Patient Global Impression of Change (PGI-C) to be administered at the 24 Week and 48 Week (EOT) visits. A total of 17 scheduled visits will take place over approximately 52 weeks.

You conducted two Phase 2 studies for the treatment of primary axillary hyperhidrosis with different treatment duration and different formulation of sofpironium bromide gel. For study BBI-4000-CL-201, the primary efficacy endpoint was the proportion of subjects achieving at least a 2-grade improvement in HDSS from baseline to end-of-therapy (EOT). For study BBI-4000-CL-203, the co-primary endpoints were the proportion of subjects with at least 1-point improvement in HDSM-Ax from baseline to EOT and the change of HDSM-Ax from baseline to EOT as a continuous measure. It should be noted that HDSM-Ax score is the mean score of 11 items and subjects must answer at least 6 of the 11 items to be evaluable for HDSM-Ax total score. Efficacy results were not consistent across the two Phase 2 studies and within each study, there was no dose response.

You plan to conduct two identical, randomized, multicenter, double-blind, vehicle-controlled, Phase 3 studies to investigate sofpironium bromide gel, 5% and 15%, in subjects with axillary hyperhidrosis. The protocol synopses specified the primary efficacy endpoint to be the composite responder success of at least (b) (4) point improvement in the HDSM-Ax score and at least 50% reduction in GSP from baseline to EOT, which you rationalized based on psychometric analysis conducted on the results from the Phase 2 studies. For the efficacy analysis of the primary and secondary endpoint, you plan to use (b) (4)

The following are general comments about your study design:

- Assessing treatment effect based on (b) (4) may be difficult to interpret (b) (4)

- You also note in the briefing document that sweat production assessments were highly variable and failed to show statistically significant reduction in GSP among treatment groups. We strongly recommend a longer period than the proposed 5-minute period for assessing GSP, as well as using more frequent assessment than just one timepoint (e.g. 3 measurements in a 24 hour period) to reduce the observed variability in the GSP measurement.

- The proposed primary endpoint should be based on: (i) the gravimetrically measured sweat production (GSP) and (ii) a fit-for-purpose Patient-Reported Outcome (PRO) instrument. For more information on the PRO, see response to Question 10.

- You are taking the risk of under-powering your Phase 3 studies by using endpoints not in agreement with the recommended endpoints.

- You may assess treatment effect at your proposed EOT, as well as at each previous timepoints you specify, provided that you adjust for multiplicity. To control Type I error rate, you should pre-specify a multiplicity adjustment plan for the testing of secondary endpoints.

- The Phase 3 protocols should specify a primary method to handle missing data for the ITT population, along with at least two sensitivity analyses that utilize alternative assumptions from those of the primary method to ensure that efficacy results are not driven by the method of handling missing data.

Question 6:
Does FDA agree that the design and primary endpoints of the proposed Phase 3 studies are adequate to demonstrate the safety and efficacy of sofpironium bromide gel for use in primary axillary hyperhidrosis?

FDA Response to Question 6:

Comments regarding your protocols:

- As previously mentioned, for the Phase 3 randomized, double-blind trials, you propose a primary endpoint which includes the proportion of subjects achieving at least a (b) (4)**-point** improvement in the hyperhidrosis disease severity measure (HDSM-Ax) score and 50% GSP reduction. Refer to Introductory Comments and response to Question 10 regarding the primary endpoint.

- In Phase 3 trials, secondary endpoints intended for labeling should be few in number, clinically meaningful and analysis of such endpoint should control for multiplicity. In addition, endpoints that rely on PRO should be validated prior to commencement of Phase 3 trials. Considerations for Agency review of clinical outcome assessment instruments (including clinician reported outcome instruments) are found in guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.*

- You propose to administer both the Dermatology Life Quality Index (DLQI) and Hyperhidrosis Quality of Life Index (HidroQOL) instruments. We recommend that you consider limiting the number of assessments administered to reduce measurement redundancy across assessments (e.g., HSDM-Ax, DLQI, HidroQOL, local tolerability assessments) and respondent burden, as well as improve data quality. If you proceed to administer the DLQI or HidroQOL, we recommend that you optimize the frequency and timing of assessments, as two assessments (baseline and end of therapy) is insufficient and will not be able to inform clinical benefit of your product.

Meeting Discussion:
See Meeting Discussion below, in Question 10.

Question 7:
Does FDA agree with the proposed plan to study two concentrations of sofpironium bromide gel (5% and 15%) in the Phase 3 studies? The rationale for the proposed dosing is described in in Sections 8.4.3.2 and 8.4.4.2.

FDA Response to Question 7:
While we encourage adequate dose ranging studies during Phase 2 as previously advised, it is acceptable to study two concentrations in your Phase 3 trials, as long as your statistical analysis plan is sufficient to achieve your objectives.

Question 8:
The projected total cumulative exposure for the development program will be well in excess of 1,500 subjects (~2,000), thus meeting the ICH E1A Guideline2. Table 15 in this briefing document provides cumulative exposure to sofpironium bromide (completed and planned).

Does FDA agree that the planned patient exposure is sufficient to evaluate the safety of sofpironium bromide gel including long-term safety for use in primary axillary hyperhidrosis?

FDA Response to Question 8:

The planned exposure appears adequate, but the safety experience of your product will be a review issue.

Question 9:
The clinical development program to support the use of sofpironium bromide gel in axillary hyperhidrosis includes two identical randomized, placebo-controlled, doubleblind Phase 3 studies. (b) (4)

Additionally, a Phase 3b, long-term, open-label safety study (one year duration) will be conducted with sofpironium bromide gel, 5% and 15%, in a 1:2 ratio to address the chronic indication of use.

Brickell also intends to complete a maximum use pharmacokinetic (MUPK) study, drugdrug interaction (DDI) study, Thorough QTc (TQTc) study, skin sensitization and irritation study, and PK/safety study in pediatric patients population aged 9-17 years (Question #11).

Does FDA agree that the overall clinical development plan should adequately support an NDA submission for sofpironium bromide gel for use in primary axillary hyperhidrosis?

FDA Response to Question 9:
See above discussion. We have the following additional comments:

- Also, see response to Question 8.

- Phototoxicity and photosensitivity of your product should be addressed. If all components of the drug product do not absorb light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible) you may request this test to be waived. An absorption spectrum of the drug product as well as the molar extinction coefficient should be provided with the initial Investigational New Drug application. Applicable absorption includes significant shoulders, as well as peaks. See the 2015 guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals.*

Clinical Pharmacology Comments
- We acknowledge that your drug developmental plan includes an ongoing maximum use pharmacokinetic (PK) study in adults, and planned drug-drug interaction (DDI) study, and pediatric maximum use PK study. For the planned studies, we will provide comments (if any) after reviewing your study protocols.

- From the PK experience in adults, we note that the systemic exposure of sofpironium bromide in healthy subjects was higher than subjects with hyperhidrosis. Based on this, we recommend that the pediatric maximal use PK study be conducted in subjects with mild hyperhidrosis. The adequacy of your study data to support an NDA submission will be a review issue.

See comments below regarding pump functionality and human factor study recommendations.

Question 10:
The Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) is a patient-reported outcome (PRO) measure of the severity of excessive sweating in patients ≥12 years old with primary axillary hyperhidrosis. It was developed for use as a primary or secondary endpoint measure in clinical studies to address concerns that the existing measures of hyperhidrosis severity (e.g., the Hyperhidrosis Disease Severity Scale) were inadequate to meet FDA requirements for well-defined and reliable outcome assessments in axillary hyperhidrosis clinical studies. A child-specific version of the instrument was similarly developed for assessment of sweating severity in patients 9 to 12 years of age.

Section 8.4.4.3 of this briefing document describes the development of HDSM-Ax PRO measure in adult and adolescent patients, including development history and hypothesized conceptual framework, qualitative research to generate measure content, and provide evidence of content validity, regulatory documentation history, and measurement properties and interpretability of the HDSM-Ax score based on the psychometric analyses performed on the two Phase 2 studies (BBI-4000-CL-201 and BBI-4000-CL-203).

Does FDA agree that the HDSM-Ax PRO measure has been adequately validated and assesses the clinically meaningful changes or effects of sofpironium bromide gel on primary axillary hyperhidrosis?

FDA Response to Question 10:
It is premature to agree without additional information from your development work. We acknowledge receipt of your psychometric analysis report BBI-4000-CL-203 dated January 30, 2018, however, it is still under review.

While not a regulatory requirement, the following comments are offered in the spirit of improving measurement and, therefore, maximizing the opportunity for your study to successfully demonstrate efficacy:

- Explore your Phase 2 data to determine whether it will be preferable to reduce items based on potential measurement redundancy as we noticed high inter-item correlations in your quantitative data.
- Recall period of the HDSM-Ax may not be optimal as it is asking patients to recall their sweating from the day before (since you woke up yesterday) which introduces susceptibility to recall error, as a patient may not reliably recall their sweating experience the day before. To minimize recall error, you may want to consider administering this instrument as a daily diary in the evening.

Because you are proposing the HDSM-Ax as a co-primary endpoint, we encourage you to request a separate meeting to further discuss your COA measurement strategy with the

Agency and gain agreement on your proposed tools and endpoints prior to starting your Phase 3 trial.

Meeting Discussion:
The sponsor inquired about using a composite endpoint, based on a patient reported outcome instrument and sweat production, versus using co-primary endpoints for assessing treatment effect. The Agency noted that agreement should be reached about the component endpoints before discussion related to composite versus co-primary endpoint. The Agency reiterated the concern that severity and duration of sweat production are both relevant for assessing efficacy, however; one might change the relative importance of the two components by having more questions on severity or duration compared to the other. The Agency defers providing feedback on the endpoint (composite vs. co-primary) until agreement is reached on the component endpoints. It should be noted that analysis of a composite endpoint usually is followed by analysis of the individual component endpoints for ease in interpreting the study findings that are based on a composite endpoint.

Question 11:
Brickell intends to submit an initial pediatric study plan (iPSP) to IND 121256 for FDA review in January 2018. The iPSP will include plans to conduct a pediatric PK study and to include pediatric patients (9-17 years old) in the planned Phase 3 studies.

In general, hyperhidrosis prevalence rates are highest among those aged 18 to 54 years (1.8% - 2.6%), whereas the lowest prevalence rates (0.1% - 0.3%) are among those younger than 12 years old (Strutton et al., 2004). A post-pubertal onset is more frequently associated with axillary hyperhidrosis and can occur in patients as young as 9 years old (Moraites et al., 2014).

As part of the PSP, Brickell plans to conduct a standalone pediatric PK and safety study in patients aged 9-17 years in the first half of 2018 in parallel with the initiation of the Phase 3 studies. Furthermore, Brickell plans to enroll children aged 9-17 years as part of the Phase 3 studies (pivotal studies and long-term safety study) to evaluate the safety and efficacy of sofpironium bromide gel in the relevant pediatric population.

Brickell recognizes that the iPSP will be under review at the time of the EOP2 meeting but would like to seek FDA's agreement on enrollment of patients aged 9 years and above in Phase 3 studies before completion of the pediatric PK study.

Clarify what age range you plan to use the HDSM-Ax child specific version (HSDM-Ax Child). In your briefing package, you state that the HDSM-Ax Child was developed for children age-9-12 years, however in your draft Phase 3 study synopsis you indicate you will administer the HDSM-Ax child specific version to subjects ages (b) (4)

FDA Response to Question 11:
Your proposal to include post-pubertal subjects nine years and age and above is reasonable pending completion of recommended non-clinical elements as described below.

A juvenile animal study should be conducted with your drug product to support the safety of subjects 9 years to less than 12 years of age in clinical trials. See response to Question 5.

Your plan to conduct a pediatric maximal use PK study in parallel with Phase 3 trials appears reasonable. Also, see response to Question 9.

Meeting Discussion:
The Agency acknowledges the request to waive children ages (b) (4) The request will be reviewed by the PeRC.

Additional DMEPA Comments
We understand that you are planning to use sofpironium to treat severe primary axillary hyperhidrosis. However, you have not submitted a comprehensive risk analysis or your plans for a Human Factors (HF) validation study.

We recommend that you conduct a comprehensive use-related risk analysis. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your metered dose pump (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

If models of the same or similar combination products exist (i.e. metered dose pump), your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*).

Additionally, if models of the same or similar combination products exist (i.e. metered dose pump), it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the aforementioned information and data, you should determine whether you need to perform a human factors (HF) validation study. If you determine that an HF validation study is not needed for your product, submit your risk analysis, comparative analyses, and justification for not conducting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on *Safety Considerations for Product Design to Minimize Medication Errors* can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

CDRH General Comments

In your future application, provide the following information to support the device constituent parts of the combination product. It is recommended that you refer to the eCTD Technical Conformance Guide published in September 2016 (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf) when determining the location of the following information within your submission.

For more information regarding cGMP requirements for combination products refer to guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products* (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

For the purposes of initiating clinical trials using your device constituent you should provide information regarding #1-4, 6, and 7 below or provide a valid risk-based justification for not providing the information prior to clinical use. With regards to #4, it is not expected that full verification testing be completed prior to use in clinical trials but baseline performance data should be provided to adequately characterize the safety of the device constituent.

Provide the following information to support the device constituent parts of the combination product:

1) A complete and detailed description of your device constituent design and delivery system, including any features and functionalities unique to your device. This should

also include engineering drawings and detailed descriptions of the individual device constituent components.

2) Detailed descriptions of the principles of operation of your device, from beginning to end of the activation process, in which you explain the mechanical drug delivery mechanisms of your device constituent for it to achieve its intended use.

3) A complete and detailed device constituent design requirements and specifications document, including design inputs and outputs in accordance with 21 CFR 820.30 design controls. Ensure that you clearly describe the acceptability of your design control inputs within the context of the intended use of your combination product. Be sure to identify the essential performance requirements of your device. The essential performance requirements of any device constituent parts are the design outputs necessary for your device constituent to safely and effectively achieve the product's intended use. The essential performance requirements of the device should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, and design of the constituent parts of the combination product. Your design requirements and essential performance requirements should consider the desired level of reliability of the product and level of risk associated with failure to meet the essential performance requirements.

   For the multiple dose metered pump we expect the essential performance requirements to include, at a minimum, the following:
   - Pump Delivery (Dose weight)
   - Gel Content Uniformity
   - Actuation Force

4) Design verification documentation. Verification testing documentation may include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design requirements of the device. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should conduct testing to verify the essential performance requirements of the combination product with the to-be-marketed version of the device constituent and the intended biologic/drug product; however, if you plan to rely on verification testing conducted with a different test fluid be sure to provide a scientific rationale for the acceptability of the test fluid as a surrogate for the intended biologic/drug product (i.e. fluid characteristics, viscosity, etc.). Valid justifications for any test results not being able to pass its acceptance criteria should be provided, if applicable. Furthermore, you should utilize enough device constituent test samples that will be statistically relevant for your performance testing.

5) Design validation documentation. Design validation documentation should be performed to ensure that the device constituent parts of the combination product meet

the intended use of the combination product as a whole. Design validation documentation may be in the form of clinical studies with the to-be-marketed presentation of the device, bridging studies that successfully validate the to-be-marketed presentation of the device constituent through clinical and/or bench top studies of the essential performance requirements of the device constituent in the context of the intended use of the combination product, literature review regarding the use of the to-be-marketed device constituent presentation in the context of the intended use of the combination product, human factors studies, and/or simulated actual-use studies. It is highly recommended that you conduct clinical studies with the to-be-marketed presentation of the combination product and capture any device constituent failures/malfunctions as part of the clinical study protocol to successfully validate the device constituent parts of the combination product.

6) Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.).

7) Biocompatibility evaluation. You should provide documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff issued in June 2016 (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf) for more details.

8) Stability and shelf-life testing. You should provide documentation that ensures the final finished combination product maintains its essential performance requirements up to the labeled date of expiry.

9) Shipping studies. You should provide documentation that ensures that the final finished combination product maintains its essential performance requirements after actual or simulated shipping.

10) Lot release specifications. Provide the lot release specifications associated with the device constituents of the combination product, including all essential performance requirements.

11) It is recommended that a traceability matrix is provided to ensure each design requirement has been adequately verified and validated. The following is an example

traceability matrix for the essential performance requirements of the device constituent as a summary of the testing completed to support the device constituents of the combination product:

Essential Performance Requirement	Specification	Verification	Validation	Shelf Life / Stability (Y/N)	Shipping / Transportation (Y/N)	Lot Release Testing (Y/N

12) As the owner of the combination product it is expected that you maintain the requirements for your product within your marketing application. If you intend to refer to documentation (e.g. verification testing) held within another submission and/or master file be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e. volume, page number, section header, etc.). It is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.

Meeting Discussion:
The sponsor inquired about the classification of the drug product as a combination product and evaluation requirements for the device (metered dose pump). The Agency stated that all metered dose pumps are classified as devices by the Agency.

As the combination product owner, the sponsor would be responsible for the cGMP requirements for combination products under 21 CFR Part 4 and follow 21 CFR Part 820.30 design controls for design requirements of the device constituent. The sponsor can refer to the master file for documentation and provide a letter of authorization for the information. However, as the owner of the combination product, the Agency expects the requirements and information requested to be submitted in a future marketing application.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints,

and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of

IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
02/07/2018