CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218158Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 128133

MEETING MINUTES

Formosa Pharmaceuticals, Inc.
c/o AimMax Therapeutics, Inc.
Attention: Laurene Wang, PhD
Chief Development Officer
4220 Apex Highway, Suite 140
Durham, NC 27713

Dear Dr. Wang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for APP13007 (clobetasol propionate ophthalmic suspension). We also refer to the teleconference between representatives of your firm and the FDA on October 31, 2022. The purpose of the meeting was to discuss the development of APP13007 (clobetasol propionate ophthalmic suspension), 0.05%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Lois Almoza, MS, Senior Regulatory Health Project Manager at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 31, 2022, from 9:00am – 10:00am (EST)
Meeting Location:	Teleconference
Application Number:	IND 128133
Product Name:	APP13007 (clobetasol propionate ophthalmic suspension)
Indication:	Post-operative Inflammation and Pain Following Ocular Surgery
Sponsor Name:	Formosa Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Lois Almoza, MS

FDA ATTENDEES

Wiley Chambers, MD	Director, Division of Ophthalmology (DO)
William Boyd, MD	Deputy Director, DO
Rhea Lloyd, MD	Clinical Team Lead, DO
Jennifer Harris, MD	Clinical Team Lead, DO
Martin Nevitt, MD	Clinical Reviewer, DO
Mukesh Summan, PhD	Director, Division of Pharmacology & Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/ /Specialty Medicine (DPT RDPURM/SM)
Maria Rivera, PhD	Pharmacology/Toxicology Reviewer, DPTRDPURM/SM
Ping Ji, PhD	Acting Clinical Pharmacology Team Leader, Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/ Division of Inflammation and Immune Pharmacology (DIIP)
Hyewon Kim, PhD	Staff Fellow, Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Solomon Chefo, PhD	Statistical Reviewer, Office of Translational Sciences (OTS)/Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Chunchun Zhang, PhD	Senior, Pharmaceutical Quality Assessor (SPQA), Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)/Division of New Drug Products III (DNDPIII)/New Drug Products Branch (NDPB) 6

Rose Xu, M. S	Senior Pharmaceutical Quality Assessor, OPQ/OPMA/DPMAIV
Sithamalli Chandramouli, PhD	Senior, Product Quality Reviewer OPQ/ONDP/DNDAPl/NDB3
Elise Luong, PhD	Product Quality Reviewer, OPQ/ONDP/ DNDPIII/NDPB6
Yeissa ChabrierRosello, PhD	Senior, Microbiology Reviewer, Office of Pharmaceutical Quality (OPQ)/ Office of Pharmaceutical Manufacturing Assessment (OPMA)/ Division of Microbiology Assessment l (DMAI)/MAB3
Yarery Smith, PhD	Product Quality Microbiology Reviewer, Office of Pharmaceutical Quality (OPQ)/ Office of Pharmaceutical Manufacturing Assessment (OPMA)/ Division of Microbiology Assessment l
Diana Willard	Chief Project Management Staff, Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Specialty Medicine (DROSM)
Lois Almoza, MS	Senior, Regulatory Project Manager, ORO/DROSM

SPONSOR ATTENDEES

Laurene Wang, PhD	Chief Development Officer
Derek Nunez, MD	Chief Medical Officer
Erick Co, PhD	Chief Scientific Officer
Thomas Lategan, PhD	Regulatory Affairs
(b) (4)	Consultant, Biostatistics
Kate Tsan, MS	CMC Project Specialist

BACKGROUND

Formosa Pharmaceuticals, Inc. submitted a meeting request on August 23, 2022, to discuss to discuss the development of APP13007 (clobetasol propionate ophthalmic suspension), 0.05%. A meeting request granted letter issued on September 13, 2022. Meeting package was received on September 29, 2022. Meeting preliminary comments issued on October 18, 2022. Talking points from the Sponsor sent via e-mail on October 25, 2022, are attached.

DISCUSSION

Following, in **bold**, are the questions submitted in the September 29, 2022, meeting package. The FDA responses to these questions are in *italics.* Discussions that took place during the October 31, 2022, teleconference are in regular font.

Chemistry, Manufacturing and Controls

1. **Does the Agency agree that the proposed drug substance (DS) tests and specifications are acceptable to support the NDA and registration of APP13007 [redacted]?**

FDA Response: The proposed drug substance tests and acceptance criteria appear to be adequate to support the NDA.

Meeting Discussion: None

2. **Does the Agency agree that the proposed drug product (DP) tests and specifications are acceptable to support the NDA and registration of APP13007 ([redacted])?**

FDA Response:

a. *For Clobetasol Propionate Identification (1) HPLC retention time (RT), use [redacted] instead of [redacted].*

Meeting Discussion: None

b. *For Total Impurities, we suggest establishing the limit based on long-term stability data and the ALARA principle (As Low As Reasonably Achievable). At the present time, we cannot comment on your proposed limit of NMT [redacted] nd it will be determined during the NDA review.*

Meeting Discussion: None

c. *Analytical methods and all other acceptance criteria appear to be reasonable.*

Meeting Discussion: None

d. *The sterility and antimicrobial effectiveness tests referenced in Table 11 of the 09/29/2022, submission (Seq. 0044) appear reasonable from a quality microbiology perspective. It is expected that the NDA submission includes a description of the specific test methods, the acceptance criteria, and validation data. The acceptability of the test methods and the validation data will be determined during the NDA review.*

Meeting Discussion: None

3. [redacted]

FDA Response: (b) (4) [redacted] (b) (4)

Meeting Discussion: The Sponsor asked if the clarification given in their meeting talking points (attached) provide adequate support for (b) (4) [redacted] (b) (4) Agency stated that this question would be a review issue and all information on this matter should be included in the NDA. If additional data was required, the Agency would request it during the NDA review.

4. **Based on the CMC information presented in Section 4 of this briefing package for the pre-NDA meeting, does the Agency have any comments, or areas of concern or requests?**

FDA Response: No additional comments at this time.

Meeting Discussion: None

Nonclinical

5. Will the Division re-confirm that the 3 pivotal nonclinical studies described above, together with other ancillary studies, that comprise the entirety of the nonclinical package are sufficient to support the NDA and registration of APP13007?

FDA Response: As previously stated, the battery of nonclinical studies appears sufficient for NDA submission. The adequacy of the submitted data to support registration will be determined during the review of your NDA.

Meeting Discussion: None

6. For product labeling purposes, the Sponsor proposes to reference some nonclinical information considered as "class labeling" for ocular corticosteroids. This includes Section 13 of the Label for carcinogenesis, mutagenesis and impairment of fertility. Does the Agency concur?

FDA Response: We recommend you primarily use information pertinent to the active ingredient. The determination of the adequacy of the information used in the label will be a review issue.

Meeting Discussion: None

Clinical

7. Are the data from the four clinical studies sufficient to support the NDA and registration of APP13007 (b) (4) for the intended indication?

FDA Response: The summary data from the four clinical studies are sufficient to support filing of an NDA for APP13007 (b) (4). The sufficiency of the data to support NDA approval is a review issue.

Meeting Discussion: None

8. For the purposes of the Integrated Summary of Efficacy (ISE) and the product label, the Sponsor intends to summarize efficacy endpoints using pooled data from the two Phase 3 pivotal trials with a total of 366 subjects in the APP13007 group and 382 subjects in the placebo group. Due to the differences in assessing primary efficacy endpoints and different dosing regimens/strengths between the Phase 2 and Phase 3 studies, the Sponsor proposes not to include the subjects from the Phase 2 study (CPN-201) in the ISE analysis. Does the Agency concur with this analysis plan for the ISE?

FDA Response: *Your plan for the ISE is acceptable. The individual clinical study reports for each study must also be included in Module 5 of the NDA submission.*

Meeting Discussion: None

9. For the sub-group analyses in the ISE, the Sponsor plans to analyze the primary efficacy endpoints in sub-groups by age (<65y and ≥ 65y), by [redacted] by race (white/non-white), and by iris color (blue/brown/other). There will not be a subgroup analysis based on the extent of study drug exposure. Does the Agency concur with this analysis plan?

FDA Response: *No. We recommend that race differentiate at a minimum between American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Please see "Collection of Race and Ethnicity Data in Clinical Trials, Guidance for Industry and Food and Drug Administration Staff" for further information. We would prefer iris color be divided between light and dark colored irides.*

Meeting Discussion: The Sponsor planned to revise the sub-group analysis plan for both the ISE and ISS to be consistent with FDA's recommendation. Additionally, the Sponsor asked if the Agency agreed for either ISE or ISS, there would not be a subgroup analysis based on the extent of study drug exposure because it is confounded by the short duration of the study drug treatment and by the fact that the study drug was stopped when a subject received rescue medication. The Agency agreed.

The Sponsor asked if the sub-group analyses for iris color in the ISE, could be based on: Dark Irides = Brown (as in eCRF) and Light Irides = Blue or Other (as in eCRF). The Agency agreed. In the ISS, the Sponsor noted there would not be a subgroup analysis of safety based on the iris color because it significantly overlapped with the race-based sub-group analysis. The Agency did not object.

10. For the purposes of the Integrated Summary of Safety (ISS) and the product label, the Sponsor intends to summarize safety endpoints using only one pooled dataset from all subjects in the two Phase 3 pivotal trials and one Phase 2 trial (both Part A and Part B with BID or BID/QD regimens for 21 days and 14 days, respectively). Does the Agency concur with this plan for the ISS?

FDA Response: *Yes. Your plan is acceptable.*

Meeting Discussion: None

11. With regard to the ISS, the Sponsor will summarize treatment-emergent adverse events (TEAEs) using pooled data for all TEAEs and, separately, pooled data for only the ocular TEAEs in the study eye. Is this acceptable?

FDA Response: *Yes. Your plan is acceptable.*

Meeting Discussion: None

12. In the ISS and for the product label, the Sponsor intends to summarize the ocular TEAEs in the study eye which occurred with an incidence of ≥ 1%. Is this acceptable?

FDA Response: *Your plan is acceptable for the ISS. The selection of adverse event reporting in the labeling will be a review issue.*

Meeting Discussion: None

13. In the ISS (b) (4) the Sponsor proposes to summarize treatment emergent IOP elevation events using the combined criteria of IOP ≥ 21 mmHg and an IOP increase of >10 mmHg from pre-dose baseline. Is this acceptable?

FDA Response: Your plan is acceptable for the ISS. (b) (4)

Meeting Discussion: None

14. For the sub-group analyses in the ISS, the Sponsor plans to summarize ocular TEAEs in the study eye in sub-groups by age (<65y and ≥ 65y), by and by race (white/non-white). There will not be a subgroup analysis based on the extent of study drug exposure. Does the Division concur with this analysis plan?

FDA Response: *No. See response to Question 9.*

Meeting Discussion: None

15. The statistical analysis plans (SAPs) for the ISE and ISS are respectively included in Appendix 2 and Appendix 3 of this document. Does the Division have any comments on either of these analysis plans?

FDA Response: *No additional comments.*

Meeting Discussion: None

16. For ISE and ISS, the Sponsor proposes to include the listings, tables, figures, appendices (including SAP), and datasets in Module 5.3.5.3, and present the

text narrative in Module 2.7.3 and Module 2.7.4, respectively. Does the Division agree with this proposal?

FDA Response: *Yes, your proposal is acceptable.*

Meeting Discussion: None

Regulatory

17. In light of the timing of the recent new Guidance for Industry on drug-device combinations for ophthalmic drug products relative to the timing of the NDA submission of APP13007, will the Division waive the designation of "APP13007 (b) (4)" as a drug-device combination product?

FDA Response: *No, in accordance with the reference in the background to this question, the FDA guidance "Certain Ophthalmic Products: Policy Regarding Compliance with 21 CFR Part 4" (the March 2022 guidance), the Agency is implementing the results of the Genus court litigation. Specifically, on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued its decision in Genus Medical Technologies LLC v. U.S. Food and Drug Administration, 994 F.3d 631 (D.C. Cir. 2021). The Genus court stated "[e]xcepting combination products. . . devices must be regulated as devices and drugs — if they do not also satisfy the device definition — must be regulated as drugs." In implementing this decision, FDA has determined that the language in § 200.50(c) indicating that ophthalmic dispensers are regulated as drugs when packaged with ophthalmic drugs is now obsolete, because these articles meet the device definition. Accordingly, your product is a single entity combination product under 21 CFR 3.2(e)(1).*

In reference to the Part 4 combination product CGMPs, as described in the March 2022 guidance, FDA is evaluating how the 21 CFR part 820 requirements as set forth in part 4 apply to combination products that include eye droppers that administer the drug directly to the eye.

Meeting Discussion: The Sponsor clarified they would identify APP13007 as a combination product on Form FDA 356h and identify all facilities involved in the manufacturing of the constituents of the drug product including the eye-drop container closure system. Per the Sponsor's QA audits, all facilities had implemented appropriate procedures in compliance with Part 4 combination product cGMPs.

From the Sponsor's assessment of their drug product-dropper bottle combination and the response from the Agency, the Sponsor understood that prior to the NDA submission no additional studies were required under the March 2022 Guidance cited in the Meeting Preliminary comments dated October 18, 2022. The Agency confirmed no additional studies were required prior to the NDA submission.

18. The Sponsor has not designated a particular clobetasol propionate containing product as a Reference Listed Drug (RLD), and therefore will not include labeling information of a reference listed drug in the NDA (i.e., Section 1.14.3). Is this approach acceptable to the Agency?

FDA Response: If you do not intend to refer to a listed drug for which you do not have the right of reference, your plan is acceptable.

Meeting Discussion: The Sponsor indicated that it had not designated a particular clobetasol propionate containing product as a listed drug (LD) because it believes there is no appropriate or relevant LD that could be designated. Any labeling information from currently available dermal products of clobetasol propionate would have little relevance to guiding the use of APP13007. The Sponsor does not propose to include labeling information of a specific LD in the NDA (i.e., Section 1.14.3), but will adopt a hybrid approach of using information from both dermal products containing clobetasol propionate as the active ingredient and ocular products containing corticosteroids, in addition to information specific to APP13007 (b) (4). The Agency stated that reference to a LD was not needed for sections of the label that provide information considered to be "general medical knowledge", as exemplified in Section 5.1 of the sample labeling text provided by the Sponsor. (b) (4) (D) (4) (b) (4) The Sponsor indicated that a nonclinical PK bridging study was performed for APP13007 in comparison to a LD, but an appropriate LD, i.e., an ointment-based dermal product, was not available in the US for the bridging study.

The Sponsor noted (b) (4) was unreliable for application on the rabbit skin in the bridging study to compare systemic exposure of clobetasol propionate between dermal and ocular routes of administration. Temovate, an ointment-based product, would be more appropriate for such study. However, Temovate has been withdrawn from the US market, for reasons other than safety or efficacy, (b) (4) The Agency remarked that if a drug product had not been withdrawn for reasons of safety or efficacy, then it could be appropriate to serve as an LD in a 505(b)(2) application. Thus, Temovate could serve as the LD for APP13007 NDA and the label for APP13007((b) (4) could cite Temovate labeling in the relevant sections.

19. The Sponsor proposes to adopt the "class" labeling for ocular corticosteroid products such as that for DUREZOL® (0.05% difluprednate) and INVELTYS® (loteprednol etabonate 1%) for the Sections on Contraindications, Warnings and Precautions, and Adverse Reactions (Label Sections 4, 5, and 6) and for the Sections on Use in (b) (4) Populations and Nonclinical Toxicology (Label Sections 8 and 13). Does the Division agree with this approach?

FDA Response: *Comments on the labeling will be deferred until submission and review of the full NDA.*

Meeting Discussion: None

20. Given the submission of the two Phase 3 clinical studies demonstrating clinical efficacy and safety of APP13007, the Sponsor anticipates that this NDA, if approved, will qualify for 3 years of market exclusivity for APP13007 (b) (4). Can the Division confirm this?

FDA Response: *Decisions regarding market exclusivity are made after NDA approval.*

Meeting Discussion: None

21. The proposed Table of Contents for the APP13007 (b) (4)) NDA is included in Appendix 4 of this document. Does the Division have any comments and/or any areas of concern or deficiency?

FDA Response: *None.*

Meeting Discussion: None

ADDITIONAL COMMENTS:

- For location of information on the device constituent part see the FDA eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" October 2021* accessible at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

- In your future submission, the Form FDA 356h should identify your product as a combination product (see form field 24). Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.

Additional Meeting Discussions:

Regarding nonclinical labeling information the Agency clarified the content and format in Section 8.1 has to comply with the Pregnancy Lactation Labeling Rule (PLLR). When the doses used in the nonclinical studies are cited in the labeling, the exposure multiples need to be provided, i.e., it needs to relate to the human equivalent dose.

The Sponsor noted the submission of their NDA is planned for March 2023.

ATTACHMENTS – Talking points from Sponsor e-mailed on October 25, 2022

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/s/

WILEY A CHAMBERS
11/30/2022 08:56:21 AM

IND 128133

MEETING MINUTES

Formosa Pharmaceuticals, Inc.
c/o AimMax Therapeutics, Inc.
Attention: Laurene Wang, Ph.D.
Chief Development Officer
4220 Apex Highway, Suite 140
Durham, NC 27713

Dear Dr. Wang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for APP13007 (clobetasol propionate ophthalmic suspension). We also refer to the telecon between representatives of your firm and the FDA on September 2, 2020. The purpose of the meeting was to discuss APP13007 (clobetasol propionate ophthalmic suspension).

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 Lois Almoza, MS, Senior Regulatory Health Project Manager at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: September 2, 2020 from 12:30pm – 1:30pm(EST)
Meeting Location: Teleconference

Application Number: 128133
Product Name: APP13007 (clobetasol propionate ophthalmic suspension)
Indication: Post-operative inflammation and pain following ocular surgery
Sponsor Name: Formosa Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Lois Almoza, MS

FDA ATTENDEES

Wiley A. Chambers, MD, Acting Director, Division of Ophthalmology (DO)
William M. Boyd, MD, Clinical Team Leader, DO
Rhea Lloyd, MD, Clinical Reviewer, DO
Guoxing Soon, PhD, Statistical Team Leader, Office of Biometrics (OB)
Solomon Chefo, PhD, Statistical Reviewer, OB
Lois Almoza, MS, Senior Regulatory Health Project Manager, Division of Regulatory Operations for Specialty Medicine
Priya Brunsdon, PharmD, Clinical Pharmacology Reviewer, Division of Inflammation and Immune Pharmacology (DIIP)
Maria Rivera, PhD, Nonclinical Reviewer, Division of Pharm/Tox of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DPT-RPURM)
Chunchun Zhang, PhD, Acting Product Quality Team Leader, Office of Product Quality (OPQ)
Helen Ngai, PhD, Product Quality Microbiology Reviewer, OPQ
Christopher Galliford, PhD, CMC Reviewer, OPQ

SPONSOR ATTENDEES

Laurene Wang, PhD, Chief Development Officer
Derek Nunez, MD, Chief Medical Officer
Erick Co, PhD, Chief Scientific Officer
(b) (4) Consultant, Biostatistics
Gary Novack, PhD, Clinical and Regulatory Affairs
(b) (4) Consultant, Regulatory Affairs and Quality Assurance

BACKGROUND

According to Formosa Pharmaceuticals, Inc., APP13007 is an ophthalmic aqueous suspension containing clobetasol propionate as the active ingredient. The placebo vehicle that does not contain clobetasol propionate will be used to match the active APP13007 suspension and is referred to as 'matching vehicle placebo' for 0.05% APP13007. The active 0.05% APP13007, a preserved multi-dose ophthalmic product, and its matching vehicle placebo product have the same appearance of an opalescent liquid.

APP13007 0.05% and the matching vehicle placebo products intended for Phase 3 clinical trial materials (CTMs) and for registration/commercialization are of the same formulation as the CTMs used in the Phase 2 clinical study CPN-201. The products will be filled in a multi-dose low density polyethylene (LDPE) 5 mL eyedropper bottle with a LDPE tip (nozzle) and tightly closed with a high density polyethylene (HDPE) cap.

DISCUSSION

Following, in **bold font**, are the questions in the July 14, 2020, Meeting Package. The FDA responses to these questions are in *italic* font. Discussions that took place during the September 2, 2020, teleconference are in regular font.

Chemistry, Manufacturing and Controls

1. **Does the Agency agree that the drug substance (DS) specifications are acceptable to support the Phase 3 clinical development program and drug product registration batches?**

FDA Response: Your proposed drug substance specifications are acceptable to support the Phase 3 clinical development program and drug product registration batches.

Meeting Discussion: None

2. **Does the Agency agree that the drug product (DP) specifications are acceptable to support the Phase 3 clinical development program and registration batches?**

FDA Response: The proposed drug product specifications appear to reasonable. The microbiology related specifications (including referenced methods and acceptance criteria) are reasonable from a product quality microbiology perspective. A complete review of batch data, including raw chromatographic data will be performed at the time of NDA submission. In addition, a detailed description of the manufacturing process, including in-process controls should be provided.

Meeting Discussion: None

3. Does the Agency agree that the proposed method and acceptance criteria [redacted] are adequate to support the Phase 3 development program and registration stability batches?

FDA Response: *The [redacted] test appears to be reasonable to ensure dose uniformity. However, data from additional timepoints would be helpful [redacted]*

Meeting Discussion: None

4. Does the Agency agree that the proposed DP stability study protocol is sufficient to support Phase 3 CTMs and registration batches?

FDA Response: *The drug product stability protocol appears to be adequate to support these planned batches. The stability program is reasonable from a product quality microbiology perspective. A detailed explanation of your extractables/leachables test should be included and these tests should be performed using the container/closure system that will be used in the intended marketed presentation(s) of your drug product. These data will then be evaluated at the time of NDA submission. Refer to USP <1663> and <1664> for recommendations.*

Meeting Discussion: None

5. The Sponsor addressed FDA's non-clinical hold comments on chemistry, manufacturing and control received on December 30, 2019 in a submission on February 7, 2020 (Serial No. 0006). Please confirm that the Sponsor's response adequately addresses FDA's comments and requests.

FDA Response: *The responses to the CMC comments appear to be reasonable.*

Meeting Discussion: None

Nonclinical

6. The Sponsor completed two GLP toxicology studies (a 14- and 28-day study, respectively) which were submitted in the initial IND (Serial No. 0001). The 28-day study evaluated the current 0.05% APP13007 clinical formulation instilled twice daily in rabbits. We consider these studies sufficient to support the Phase 3 trials. Does the Agency concur?

FDA Response: *Agree.*

Meeting Discussion: None

7. The Sponsor intends to conduct a nonclinical ocular tissue pharmacokinetic (PK) study of the 0.05% clinical formulation of APP13007 prior to NDA submission. Together, this study and the two GLP toxicology studies conclude the nonclinical development of APP13007 and the Sponsor considers that data from these studies are sufficient to support the NDA and registration of 0.05% APP13007 under the 505b(2) regulatory pathway. Does the Agency concur?

FDA Response: The battery of nonclinical studies appears sufficient for NDA submission. However, the adequacy of the submitted data to support registration will be determined during the review of your NDA.

Meeting Discussion: None

8. The Sponsor addressed FDA's non-hold issues for nonclinical studies received on December 30, 2019 in a submission on February 7, 2020 (Serial No. 0006). Please confirm that the Sponsor's response adequately addresses FDA's issues and questions.

FDA Response: Agree. However, for future studies/applications, we recommend conducting the ERG examinations according to the standards of the International Society for Clinical Electrophysiology of Vision, with the needed modifications for the animal model. The exam is constituted of five responses: rod response; maximal response in the dark-adapted eye; oscillatory potentials; light adapted cone response; and responses to a 30-Hz flickering stimulus.

Meeting Discussion: None

Clinical

9. Based upon the results of evaluating three dosing regimens (varying dose strength, frequency and duration) in Study CPN-201, the Sponsor has selected 1 drop of 0.05% APP13007 administered BID for 14 days as the dosage regimen for the Phase 3 pivotal clinical studies. Does the Agency concur that the study results of Study CPN-201 support the selection of this dosage regimen for Phase 3 development?

FDA Response: Yes, your proposed dosing regimen is acceptable.

Meeting Discussion: None

10. In support of a potential NDA for the indication of treatment of post-operative inflammation and pain following ocular surgery, the Sponsor proposes to

conduct two identical Phase 3, double-masked, parallel-group, placebo vehicle-controlled studies in post-cataract surgery patients who fulfill the inclusion and exclusion criteria summarized in the Protocol Synopsis of the Phase 3 trials to achieve the intended indication of APP13007. Does the Agency concur?

FDA Response: Yes, your proposal is acceptable. Only a protocol synopsis was submitted. Additional comments may be forthcoming when the full protocol and statistical analysis plan are received.

Meeting Discussion: None

11. In the planned Phase 3 studies, the Sponsor proposes the Primary Efficacy endpoints to be (i) the proportion of subjects with ACC Count = 0 (ACC Grade = 0) at Day 8 after cataract surgery (POD8), maintained through post-operative Day 15 (POD15), and (ii) the proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15. Does the Agency concur?

FDA Response: Yes, your proposed primary efficacy endpoints are acceptable.

Meeting Discussion: The Sponsor proposed treating "Rescued subjects" as "Non-Responders" to the study drug. The Agency agreed that this is a possible approach, but stated that the clinical parameters used to establish that a subject is to be rescued should be defined in the protocol. An explanation should be included in the clinical study report and the parameters at the time of rescue should be recorded to confirm the validity of the rescue.

The Sponsor proposed discontinuing rescued subjects from study drug and from the study at the time of rescue. The Agency stated that this approach was not preferred and that rescued subjects should be continued in the study for follow up, including adverse events may later emerge. Evaluations for these subjects should be included in the safety results.

The Sponsor proposed using LOCF to impute missing data for the primary analyses for subjects who discontinue from the study, including rescued subjects. The Agency stated this approach is acceptable, but the Sponsor should also conduct additional analyses, including analyses using just observed data on study.

12. In each of the two planned Phase 3 studies, the Sponsor proposes to evaluate approximately 350 post-cataract surgery patients, randomized in a 1:1 ratio to 0.05% APP13007 and matching vehicle placebo. With this proposed sample size, the Sponsor estimates that approximately 372 post-cataract surgery patients would have been exposed to 0.05% APP13007 BID for at least 14 days, and approximately 428 subjects would be exposed to APP13007 at any dose strength, frequency and duration throughout the clinical development of APP13007. The Sponsor considers that this sample

size is adequate to support the safety profile of 0.05% APP13007 for NDA/registration. Does the Agency concur?

FDA Response: *Your proposed safety population appears acceptable.*

Meeting Discussion: None

13. In the planned two Phase 3 studies together, the Sponsor proposes to evaluate a total of 100 patients on active drug and 50 on matching vehicle placebo for corneal endothelial cell assessments at baseline and at three months following the initiation of the 2-week treatment. Does the Agency concur?

FDA Response: *Concur.*

Meeting Discussion: None

14. Continuing from Question #5 above, alternatively, can corneal endothelial cell assessments be conducted in healthy volunteers instead of post-cataract surgery patients? If so, what is the recommended sample size?

FDA Response: *Yes. We recommend at least 100 subjects exposed to study drug with a concurrent control (no more than 2:1 randomization) treated for at least as long as indicated and followed for at least 3 months.*

Meeting Discussion: None

15. In Study CPN-201, no clinically meaningful treatment-related effects on the clinical laboratory parameters, including clinical chemistry, hematology and serum cortisol, were observed following administration of 0.05% APP13007 BID for 21 days, thus the Sponsor proposes not to conduct clinical laboratory evaluation in the pivotal Phase 3 trials. Does the Agency concur?

FDA Response: *Concur.*

Meeting Discussion: None

16. In addition to the two Phase 3 trials, the Sponsor is currently conducting a clinical PK study to evaluate the systemic exposure to the active ingredient of APP13007, CP, in healthy subjects over a 24-hour period following ocular instillation of the first drop and then after the second drop of 0.05% APP13007 administered approximately 12 hours apart.

The Sponsor does not plan to conduct any additional clinical studies and considers that data from these studies (two Phase 3 pivotal studies, one Phase 2 dose-selection study and a Phase 1 systemic exposure study) will

be sufficient to support the NDA of 0.05% APP13007 for the intended indication. Does the Agency concur?

FDA Response: *The proposed two Phase 3 clinical studies, the Phase 2 dose-selection study and the Phase 1 systemic exposure study should be sufficient to support an NDA for 0.05% APP13007. The systemic PK of the final to-be-marketed formulation at the intended clinical dose should be characterized prior to NDA submission.*

Meeting Discussion: The Agency acknowledged its typographical error for 0.05% APP13007 which read 0.5% in the Meeting Preliminary Comments provided.

The Sponsor emphasized that the clinical PK study was conducted using the final-to-be marketed formulation. The study characterized the systemic PK after BID daily dose as in the planned pivotal Phase 3 clinical trials. The Sponsor noted the data are available and show that (i) very few samples have measurable concentrations above LLOQ, (ii) when measurable the levels are low and quickly decay to below LLOQ, and (iii) there is no evidence of accumulation. Thus, the Sponsor considered the design of the Study CPN-102 adequate to characterize the systemic PK at the intended clinical dose and no further clinical study was required. The Agency agreed and stated that it was reasonable not to conduct further PK studies. The clinical and bioanalytical study reports would be expected to be submitted to the NDA.

17. **The Sponsor addressed FDA's non-hold comments received on December 30, 2019 in a submission on February 7, 2020 (Serial No. 0006). Please confirm that the response addresses FDA's comments.**

FDA Response: *The responses addressed our comments.*

Meeting Discussion: None

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*.[1] 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.[2]

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.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The

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[1] 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.

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

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

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

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

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

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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