CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217370Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 147005

MEETING MINUTES

Aerie Pharmaceuticals, Inc.
Attention: George Baklayan
Sr. Director Regulatory Affairs/Technical Writing
20511 Lake Forest Drive
Lake Forest, CA 92630

Dear George Baklayan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Acoltremon (AR-15512) ophthalmic solution. We also refer to the video conference between representatives of your firm and the FDA on March 4, 2024. The purpose of the meeting was to discuss the format and content of your future NDA application.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions contact Nick Connis, Regulatory Project Manager, at Nick.Connis@fda.hhs.gov or call (301) 796-0382.

Sincerely,

{See appended electronic signature page}

Charles Ganley, MD
Director
Office of Specialty Medicine
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: March 4, 2024, 1:00 PM – 2:00 PM (EST)
Meeting Location: Virtual Meeting

Application Number: IND 147005
Product Name: Acoltremon (AR-15512) ophthalmic solution
Indication: Treatment of dry eye disease
Sponsor Name: Aerie Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic

Meeting Chair: William Boyd, MD
Meeting Recorder: Nick Connis, MS

FDA ATTENDEES

Charles Ganley, MD	Director, Office of New Drugs (OND)/Office of Specialty Medicine (OSM)
Alex Gorovets, MD	Deputy Director, OND/OSM
William Boyd, MD	Deputy Director, OSM/Division of Ophthalmology (OSM/DO)
Rhea Lloyd, MD	Clinical Team Leader, OSM/DO
Shilpa Rose, MD	Clinical Reviewer, OSM/DO
David Summer, MD	Clinical Reviewer, OSM/DO
Jennifer Hammer, MD	Clinical Reviewer, OSM/DO
Julie Kim, MD	Clinical Reviewer, OSM/DO
Kimberly Hatfield, PhD	Supervisor, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine (DPT-RPURM)
Muriel Saulnier, DVM, PhD	Pharmacology/Toxicology Reviewer, DPT-RPURM/SM
Bindi Nikhar, MD	Associate Clinical Director, Office of the Commissioner (OC)/ Office of Clinical Policy, and Programs (OCPP)/ Office of Combination Products (OCP)
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
Milton J. Sloan, PhD	Senior, Product Quality Reviewer, OPQ/ ONDP/ DNDPIII/ NDPB6

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)
Amit Somani, PhD	Senior Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Thamban Valappil, PhD	Supervisor, Mathematical Statistician, Office of Translational Sciences (OTS)/Office of Biostatistics (OB)/Division of Biometrics IV (DBlV)
Greg Soon, PhD	Statistics Team Leader, OTS/OB/DBIV
Fraser Smith, PhD	Statistics Reviewer, OTS/OB/DBlV
Epiphanie Nyirabahizi, PhD	Statistical Reviewer, OTS/OB/DBIV
Valerie Vaughan, PharmD	Team lead, Office of Surveillance and Epidemiology (OSE)/ Office of Medication Error Prevention and Risk Management (OMEPRM)/Division of Medication Error Prevention and Analysis 1(DMEPA1)
Sofanit Getahun, PharmD, BCPS	Pharmacist, OSE/ OMEPRM/ DMEPA1
Daniel Schu, PhD	Senior Microbiology Reviewer, Office of Pharmaceutical Quality (OPQ)/ Office of Pharmaceutical Manufacturing Assessment (OPMA)/ Division of Microbiology Assessment l (DMAI)/MAB3
Judit Milstein	Director, Project Management Staff, Office of Regulatory Operations / Division of Regulatory Operations for Specialty Medicine (ORO/DROSM)
Diana Willard	Chief, Project Management Staff, ORO/DROSM
Dheera Semidey, PharmD, MS, RAC	Senior Regulatory Project Manager, ORO/DROSM
Michael Puglisi, BS	Regulatory Project Manager, ORO/DROSM
Dung Tran, MAT	Regulatory Project Manager, ORO/DROSM
Nick Connis, MS	Regulatory Project Manager, ORO/DROSM

AERIE PHARMACEUTICALS, INC. ATTENDEES

Joe Rappon	VP Pharmaceutical Research and Development
Mike Son	VP Regulatory Affairs, Ocular Health
Michelle Senchyna	Scientific Advisor
Niyi Adewale	Head, Statistics
Tom Valencia	Director, Global Medical Safety
George Baklayan	Sr. Director, Regulatory Affairs/Technical Writing
Rekha Rangarajan	Project Lead
Pooja Vatsyayan	Senior Director, Global Head- Pharmaceutical Commercial Strategy and Development

Carmen Rice	Associate Director, R&D Portfolio Management and Design Control
Yvonne Nelson	Manager, Regulatory Affairs

BACKGROUND
The purpose of the meeting is to discuss the development plan of acoltremon (AR-15512) Ophthalmic Solution and the format and content of an anticipated New Drug Application (NDA). FDA sent Preliminary Comments to Aerie Pharmaceuticals, Inc. IAerie) on February 26, 2024, and on February 29, 2024, Aerie responded that during the meeting they would like to further discuss questions 5 and 9.

DISCUSSION
For the purposes of this response, the questions submitted in the Meeting Package are in **bold** font, the Division's preliminary comments are in *italics* font, and the meeting discussions are normal font.

Product Quality

Question 1: Does the Agency agree with the proposed commercial specification for acoltremon (AR-15512) including proposed changes?

FDA Response to Question 1: Yes, the Agency agrees with the proposed specification including the proposed changes.

Meeting Discussion: None.

Question 2: Does the Agency agree with the proposed commercial specifications for Acoltremon (AR-15512) Ophthalmic Solution 0.003% including proposed changes?

FDA Response to Question 2: The proposed drug product specifications appear reasonable. However, based on the evaluation of the data presented in the NDA for a regulatory approval, additional tests and/or tightening of the acceptance criteria may be recommended.

Meeting Discussion: None.

NONCLINICAL

Question 3: Does the Agency agree that the proposed nonclinical testing strategy is adequate to support the NDA for Acoltremon (AR-15512) Ophthalmic Solution 0.003%?

FDA Response to Question 3: While the completed nonclinical studies appear adequate to support the NDA submission, a final determination on acceptability for approval will be made at the time of the NDA review.

Meeting Discussion: None.

Question 4: Does the Agency agree that on the basis of negligible systemic (plasma) exposure to acoltremon and the absence of drug-related systemic toxicity in chronic ocular toxicology studies in rabbits and dogs following topical ocular administration of Acoltremon Ophthalmic Solution are considered sufficient to request waivers for rodent carcinogenicity and developmental and reproductive toxicology studies for the Acoltremon (AR-15512) Ophthalmic Solution 0.003% NDA?

FDA Response to Question 4: We agree in principle, pending review of the data and your justification for waiving those studies. We recommend that your waivers include a thorough discussion of the risk based on the drug class, pharmacological activity, pharmacokinetics in humans and animals, genotoxicity, and toxicity results, clinical safety findings, as well as supportive information from the literature as appropriate.

Meeting Discussion: None.

CLINICAL

Question 5: Does the Agency agree that the proposed efficacy data can serve as the basis for the Acoltremon (AR-15512) Ophthalmic Solution 0.003% NDA for the indication of "treatment of the signs and symptoms of dry eye disease"?

FDA Response to Question 5: Whether the proposed efficacy data can serve as the basis for the indication of treatment of the signs and symptoms of dry eye disease will be a review issue. The submitted summary information in the background materials appear to support NDA filing for acoltremon (AR-15512) Ophthalmic Solution 0.003%.

Meeting Discussion: Aerie requested clarification of the Agency response and whether Aerie's proposed clinical trials are adequate to support an NDA submission for the treatment of the signs and symptoms of dry eye disease. The FDA stated that adequacy of the data is a review issue and that this question cannot be addressed until the NDA is submitted and reviewed..

Question 6: Does the Agency agree with the Sponsor's proposal (b) (4) **for Acoltremon (AR-15512) Ophthalmic Solution 0.003% NDA?**

FDA Response to Question 6: No. Evaluation of the totality of the data will be a review issue. (b) (4) *Efficacy for a sign and efficacy for a symptom do not have to be demonstrated in the same clinical trial, but each should be demonstrated in more than one clinical trial.*

(b) (4) *. A statistically significant treatment group difference in the change from baseline in SANDE symptom score was only demonstrated in COMET-2. Your phase 2 study, COMET-1, failed its primary endpoint; thus, the secondary endpoints including change from baseline in SANDE score cannot be evaluated. In COMET-3, the change from baseline in SANDE score at Day 28 was not statistically significant.*

Meeting Discussion: None.

Question 7: Does the Agency agree with the Sponsor's proposal (b) (4) (b) (4) (b) (4) **in the eventual label for Acoltremon (AR-15512) Ophthalmic Solution 0.003% NDA?**

FDA Response to Question 7: Labeling is a review issue that can only be determined after an NDA is submitted and reviewed. See response to Question 6.

Meeting Discussion: None.

Question 8: Does the Agency agree with the Sponsor's proposal (b) (4) **for the Acoltremon (AR-15512) Ophthalmic Solution 0.003% NDA?**

FDA Response to Question 8: (b) (4) *Prespecified agreed-upon efficacy endpoints which demonstrate clinical and statistical significance and are replicated may be included in labeling.*

Meeting Discussion: None.

Question 9: Does the Agency agree with the selection of studies to include in the ISS, including the proposal to exclude the long-term safety study from the initial NDA submission?

FDA Response to Question 9: Disagree. The long term safety study data should be included in the ISS in the original NDA submission.

In addition, we recommend you submit the clinical pharmacology information including the clinical PK study report for Acoltremon (AR-15512) Ophthalmic Solution 0.003% at the time NDA submission.

Meeting Discussion: The Agency stated that the NDA should be complete when submitted. It is not the current division leadership recommendation that COMET-4 be submitted in the 120-Day Safety Update. However, the company apparently discussed this with Dr. Chambers prior to his retirement and he agreed that it was acceptable. If this is so, the safety study should be reported in the 120 safety update to the application. (see additional post-meeting comment)

The Agency requested that Aerie submit completed pharmacokinetic (PK) data at the time of NDA filing. Aerie agreed and will include the PK study report upon initial NDA filing and will also update their Investigator's Brochure with human PK data in the March, 2024, annual report to the IND.

Regarding the safety study, Aerie stated that to date, a minimum of 100 patients have been observed for at least 12 months. Aerie will submit specific numbers when their meeting minutes are submitted to the file.

Question 10: Does the Agency agree that the long-term safety study data can be submitted as a standalone report within the 120-day safety reporting period?

FDA Response to Question 10: Disagree. Refer to the response to Question 9.

Meeting Discussion: None.

Question 11: Does the FDA agree with the proposal to update only the integrated summary of Adverse Events with data from this long-term safety study?

FDA Response to Question 11: Disagree. Refer to the response to Question 9.

Meeting Discussion: None.

REGULATORY

Question 12: Does the Agency agree that should Human Factors validation study for Acoltremon (AR-15512) Ophthalmic Solution 0.003% be required, any conclusions can be submitted as a minor amendment when available during the course of NDA review?

FDA Response to Question 12: Please refer to the HF Advice Letter issued on February 13, 2024, which includes the Agency's conclusion that results of a human factors

validation study do not need to be submitted with your future marketing application for acoltremon (AR-15512) ophthalmic solution 0.003%.

Meeting Discussion: None.

Question 13: Due to the limited size of the single-use vial and required information per FDA guidance, does the Agency agree with the proposals for elements to be displayed on the vial and the pouch, including additional information important to the safe use of Acoltremon Ophthalmic Solution 0.003%?

FDA Response to Question 13: Please note, the immediate container labels must meet all applicable labeling requirements as described in 21 CFR 201.10(i) and 21 CFR 201.25. You may consider including the manufacturer's information on a label affixed to the opposite side of the vial tail. For additional information, see FDA guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors[1].

Furthermore, the acceptability of your proposed product's label and labeling will be a review issue at the time of NDA submission.

Meeting Discussion: None.

Question 14: Does the Agency agree that Acoltremon (AR-15512) Ophthalmic Solution 0.003% would not be a potential candidate for an Advisory Committee meeting during NDA review?

FDA Response to Question 14: The decision to hold an Advisory Committee meeting is made during the NDA review.

Meeting Discussion: None.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Additional Agency Comments:

1. *As acknowledged in the briefing package, the proposed acoltremon (AR-15512) Ophthalmic Solution 0.003% is a combination product subject to 21 CFR Part 4 cGMP requirements. Related Guidance is available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products.*

2. *In your future IND submission, Form 1571 should identify your product as a combination product (see form field 13). In your future NDA submissions, FDA Form 356h should identify your product as a combination product (see form field 24); the combination product Type will depend on the final to-be-marketed configuration. 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.*

3. *Part 3 combination products are subject to post-market reporting safety requirements per 21 CFR Part 4.B. For more information on post-market safety reporting requirements for combination products, see: https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.*

4. *We acknowledge that the design and analysis of your clinical trials is almost finalized, we request that you clearly specify the primary estimand of the study outlining how you have decided to handle subjects with intercurrent events. Please refer to the ICH-E9 (R1) 1 addendum for further read on estimands and how to account for different intercurrent events. Our recommendations are:*

    - *For patients without intercurrent events, use a placebo-controlled multiple imputation approach to handle missing data.*

    - *For patients who discontinued the treatment due to AE and lack of efficacy, use the treatment policy strategy including observed outcome.*

    - *Patients who receive rescue medication should be handled using a composite strategy in which, subjects with these events will be considered as non-responders. Also, they should collect safety and efficacy outcomes at all schedule study visits for all subjects including subjects who discontinue the study medication and those who receive rescue and/or prohibited medications.*

- *Note that efficacy outcomes data collected after subjects receive rescue therapy/or prohibited medications should only be used in the sensitivity analysis.*

5. *We have the following recommendations for additional analyses:*
   - *Provide plots of the mean change from baseline by treatment group and visit including the number of subjects used at each visit by treatment group.*
   - *Please perform sensitivity analyses using treatment policy strategy, and a tipping point analysis of the 2 X, 3 X, 4 X, … the vehicle control rate.*

6. *We note in COMET-2 and COMET-3 the increased incidence of instillation site burning or stinging in the acoltremon group vs. vehicle, 52.2% vs. 3.8% and 50.9% vs. 3.0%, respectively (pg. 15 of 98). Please clarify if the adverse reaction occurred only on instillation and how long the stinging/burning lasted.*
   - *We request additional details of the Schirmer testing which is described in the submitted protocol as being in the Manual of Procedures. The Manual of Procedures should be submitted to the IND.*
   - *Please provide a description of how the Schirmer tests were performed at the baseline visit, i.e., the order in which the anesthetized and unanesthetized Schirmer tests were performed.*
   - *Table 12 and 13 in the Background Materials list Baseline (Day 1) Schirmer information as "pre-drop" in the title but "post-drop" in the body of the table. Please clarify when the baseline Schirmer Test was performed relative to the dosing of study drug.*

7. *120 Day Safety Update. If the long-term safety study is not included in the original submission or in the 120 day safety update but is submitted at a later date, the Agency may choose not review it as part of the original application review cycle unless it is in response to an information request.*

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	April 3, 2024

ATTACHMENTS AND HANDOUTS

No attachments for the meeting summary.

ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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.

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

- 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, 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[6] https://www.fda.gov/media/85061/download

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/

CHARLES J GANLEY
03/26/2024 11:51:47 AM
signed on behalf of Dr. Boyd

IND 147005

MEETING MINUTES

Aerie Pharmaceuticals, Inc.
Attention: Mr. George Baklayan
Director, Regulatory Affairs/Technical Writing
2030 Main Street, Suite 1400
Irvine, California 92614

Dear Mr. Baklayan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AR-15512 ophthalmic solution. We also refer to the telecon between representatives of your firm and the FDA on January 28, 2022. The purpose of the meeting was to discuss the planned Phase 3 development program for AR-15512 for the treatment of dry eye disease.

A copy of the official minutes of the 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 Wendy Streight, PhD, Regulatory Health Project Manager at 240-402-6498.

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: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: January 28, 2022, 1:00 PM – 2:00 PM (EST)
Meeting Location: Teleconference

Application Number: IND 147005
Product Name: AR-15512 ophthalmic solution

Indication: treatment of dry eye disease
Sponsor Name: Aerie Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Wendy Streight, PhD

FDA ATTENDEES

Charles Ganley, MD	Director, Office of New Drugs (OND)/Office of Specialty Medicine (OSM)
Alex Gorovets, MD	Deputy Director, OND/OSM
Wiley Chambers, MD	Director, Division of Ophthalmology (DO)/OSM
William Boyd, MD	Deputy Director, DO/OSM
Rhea Lloyd, MD	Clinical Team Leader, DO/OSM
David Summer, MD	Clinical Reviewer, DO/OSM
Martin Nevitt, MD	Clinical Reviewer, DO/OSM
Shilpa Rose, MD	Clinical Reviewer, DO/OSM
Lori Kotch, PhD	Nonclinical Supervisor, Pharmacology/Toxicology, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
Muriel Saulnier, PhD	Pharmacology/Toxicology Reviewer, DPT-RPURM/SM
Shiny Mathew, PhD	Acting Deputy Division Director, DPT-RPURM/SM
Greg Soon, PhD	Statistics Team Leader, Office of Biostatistics/Division of Biometrics IV
Chunchun Zhang, PhD	Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)/New Drug Products Branch 3 (NDPB-3)
Zhengfu Wang, PhD,	Senior Pharmaceutical Quality Assessor, OPQ/ONDP/ DNDAPI/NDB3
Milton Sloan, PhD	Senior Product Quality Reviewer, OPQ/ONDP/NDPB3

Daniel Schu, PhD	Product Quality Microbiology Reviewer, OPQ/Office of Process Facilities/Division of Microbiology Assessment Branch 3
Suneet Shukla, PhD	Clinical Pharmacology, Acting Team Lead, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)
Amit Somani, PhD	Clinical Pharmacology, Reviewer OCP/DIIP
Wendy Streight, PhD	Regulatory Health Project Manager, Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Specialty Medicine (DROSM)
Oyinlola Fashina PharmD	Senior Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)/Project Management Staff
Sofanit Getahun, PharmD, BCPS	Safety Evaluator, OSE/Division of Medication Error Prevention and Analysis 1
Bindi Nikhar, MD	Associate Clinical Director, Office of the Commissioner, Office of Combination Products, Office of Clinical Policy and Programs

AERIE ATTENDEES

Marvin Garrett	Vice President, Regulatory Affairs and Quality Assurance
Leon Atencia	Senior Director, Regulatory Affairs
George Baklayan	Director, Regulatory Affairs
Avery Funk	Manager, Regulatory Affairs
Hilary Schwind	Manager, Regulatory Affairs
David Hollander	Chief Research & Development Officer
Michelle Senchyna	Vice President, Clinical Development and Medical Affairs
Kevin Kerr	Sr. Director, Clinical Development
Jeff White	Vice President, Research & Discovery
Ken Ruettimann	Vice President, Manufacturing
Mike McClure	Senior Director, API Manufacturing
Meg Thompson	Senior Director, Analytical Chemistry
Sally Evans	Director, Drug Product Manufacturing
Erik Pacyniak	Director, Toxicology and Drug Disposition
Finbar O'Neill	Vice President, Global Quality
Randi Rohlman	Director, Global Quality Systems & Lifecyle Support
Christopher Cook	Sr. Analytical Scientist

BACKGROUND

Aerie Pharmaceuticals, Inc. (Aerie) is currently developing AR-15512 ophthalmic solution for the treatment of the signs and symptoms of dry eye disease. Aerie submitted a meeting request on October 27, 2021. A Meeting Request Granted letter was sent to Aerie on October 29, 2021, and the meeting package was submitted to the Agency on December 9, 2021. The Meeting Preliminary Comments were sent to Aerie on January 19, 2022, and on

January 24, 2022, Aerie provided the Agency with their response to our meeting comments requesting to focus the discussion on CMC Questions 7 and 9a, 9c, 9d, Nonclinical Question 12 and Clinical Questions 13, 17a, 23, 24 and 25.

DISCUSSION

Following, in **bold,** are the questions submitted in the December 9, 2021, meeting package. The Agency's response to these questions is in *italics,* Aerie's response to the Agency's comments can be found in the Attachments and Handout section, and the meeting discussion is in normal font.

PRODUCT QUALITY

1. **Does the Agency agree with the proposed designation for drug substance starting materials i.e., (b) (4)?**

   FDA Response: *Yes, (b) (4) are acceptable as starting materials for the manufacture of drug substance AR-15512. As a reminder, a final determination regarding acceptability of starting materials will be made at the time of NDA review based on your justifications for the starting material in line with the ICH Q11 general principles as clarified in the ICH Q11 Questions and Answers Guideline, the provided specifications, batch history, control strategies of the potential and actual impurities, and their corresponding fate/purge data.*

   Additional purification steps of starting material(s) should be included as part of the description of the drug substance manufacturing process. Specifications should normally be provided for both incoming and purified starting material. All starting material specifications should include tests and justified acceptance criteria for specified impurities, unspecified impurities and total impurities. Limits for impurities should be justified by spiking experiments and demonstration of downstream purging to levels that do not impact the impurity profile of the drug substance (i.e., to less than the ICH Q3A identification threshold for non-mutagenic impurities and 30% of the ICH M7 "threshold of toxicological concern" for mutagenic impurities). We refer you to Section 5.12 of the ICH Q11 Questions and Answers Guideline for considerations regarding starting material specifications.

   Meeting Discussion: No further discussion was required.

2. **Does the Agency agree with the proposed control strategy outlined for potential impurities, including potential mutagenic impurities?**

   FDA Response: *Yes, your proposed control strategy looks reasonable.*

   Meeting Discussion: No further discussion was required.

3. **Does the Agency agree that the proposed specification tests and limits for release of the AR-15512 drug substance are appropriate for the current phase of development (Phase 3)?**

   FDA Response: The proposed quality attributes in the specification of the drug substance are reasonable for the current phase of development. The proposed acceptance criteria and impurity profile will be evaluated when your NDA is submitted. To establish drug substance specification, you are referred to ICH guidelines: Q3A (Impurities in New Drug Substances), Q3C (Impurities: Residual Solvents), and Q3D (Elemental impurities), M7 (Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk), Q11 (Development and Manufacture of Drug Substances), and Q11 Questions & Answers.

   Meeting Discussion: No further discussion was required.

4. **Does the Agency agree that the proposed specification tests and limits for release of the AR-15512 drug product are appropriate for the current phase of development (Phase 3)?**

   FDA Response: The proposed drug product specifications in general seem reasonable at this stage of development. However, additional tests and/or tightening of the acceptance limits may be required based on the evaluation of the data presented for a regulatory approval.

   As your development proceeds toward an NDA, please consider the following recommendations:
   a) *Please conduct a weight loss test to assess the moisture transmission properties of the container closure system (CCS) and the protective properties of any secondary packaging used. Please include information on the test methods used and acceptance criteria.*
   b) *Please conduct the following additional one-time tests: photostability studies per ICH Q1B and freeze/thaw temperature cycling study (3 cycles)*
   c) *While the proposed specification tests and limits for release of the AR-15512 drug product appear reasonable from a product quality microbiology perspective to support the Phase 3 clinical study we recommend the following guidances for additional information relating to the future NDA submission:*
      i) *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994).*
      ii) *Guidance for Industry:* (b) (4)

   We also recommend you request a pre-NDA CMC-dedicated meeting to discuss any outstanding CMC issues.

Meeting Discussion: No further discussion was required.

5. **Does the Agency agree to the omission of a test for [redacted] purity from the release and stability specifications for the drug product?**

FDA Response: Please continue the on-going preliminary drug product stability data up to the proposed expiry period to demonstrate the [redacted] is not formed on storage. A review determination may be premature prior to results of stability data results. Analytical procedures should be fully validated and stability indicating.

Meeting Discussion: No further discussion was required.

6. **Does the Agency agree with the proposed approach in the qualification of a secondary supplier of LDPE [redacted]?**

FDA Response: The sponsor proposes to conduct the registration stability studies on two batches filled in [redacted] units and one batch filled in the [redacted] units. The approach appears reasonable for the secondary [redacted] supplier. ICH guidance (Q1A(R2)) indicates two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified. Qualification should include meeting applicable USP tests, and adequate DMF information if referenced.

Meeting Discussion: No further discussion was required.

7. **Does the Agency agree with conducting the registration stability studies on batches stored in the horizontal orientation only through the proposed shelf-life of the product?**

FDA Response: Yes, we agree with your proposal to conduct the registration stability studies on 3 batches stored only in the horizontal worst-case orientation throughout the proposed shelf-life of the product.

Also, we recommend you perform stability studies under lower relative humidity (25℃/40%RH and 40℃/25%RH) since the proposed product is packaged in a semipermeable container (ICH Q1A(R2)).

Meeting Discussion: Aerie agreed to conduct their studies with the product in the horizontal position but asked for clarification regarding the Agency's recommendation for accelerated storage conditions of 25°C/ 40% RH. Specifically, Aerie asked if the Agency considers the container closure system of primary LDPE [redacted] units plus secondary aluminum foil pouch to be semi-permeable or impermeable. The Agency stated that liquids are stressed in low humidity conditions, not high humidity conditions. The Agency stated that although the pouch material is impermeable, data

should be obtained on the adequacy of the seal; in particular, the seal integrity of the pouch at the lower RH.

8. **Does the Agency agree with conducting a leachables study on one registration stability batch per (b) (4) source, in the worst-case horizontal orientation, throughout the proposed shelf-life of the product?**

   FDA Response: *Your approach to the extractable/leachable assessment using a representative lot of drug product, manufactured in each of the proposed LDPE (b) (4) appears reasonable. The extractable/leachable assessment on the CCS (including primary and, secondary packaging components such as inks, adhesives, etc., should provide a risk assessment in support of your study approach, refer to USP <1663> and <1664> for recommendations.*

   Meeting Discussion: No Discussion was required.

9. **Aerie proposes the commercial product label allow for patients to store and use the drug product at room temperature. The proposed submission strategy for stability data is provided in the Aerie Position below.**

   a. **Does the Agency agree that this proposed combination of data can support a projected shelf-life that includes an in-use patient storage at a temperature up to 25°C for 1 (b) (4) months?**

   FDA Response: *Aerie proposes a (b) (4) month commercial shelf-life at (b) (4) storage, followed by patient storage at room temperature for 1 (b) (4) months. Aerie proposes to evaluate the stability of the drug product when (b) (4) (b) (4) stored at 25°C/40% RH for 1 (b) (4) months (b) (4)*

   No, while simulated in-use stability study may be used to assess the moisture transmission properties of the container closure system (CCS) and the protective properties of the secondary packaging we expect the duration of the room temperature conditions to have a safety margin, preferably twice the recommended duration of time.

   Meeting Discussion: Aerie stated that they believe the recommended two-times safety margin for in-use storage is excessive and stated that they plan to conduct the in-use studies for at least the intended in-use period or greater to support the duration that will be specified on the label. Aerie stated the in-use study provided will not be the only 25° data they will be submitting. They will also have 6 months accelerated stability data on the 3 registration batches of (b) (4) units stored in the pouches. Aerie

asked if their in-use protocol will adequately support an in-use commercial label. The Agency disagreed. The Agency's general expectation for a safety margin in these circumstance has been a doubling of the time and that the currently proposed (b) (4) will not be sufficient. The Agency recommended that Aerie assess the stability for 30, 60, 90, and 120 days and include at least an extra 30 days margin.

The Agency suggested adding a control arm with the closed pouch for the in-use study. Aerie stated that they plan to run the accelerated stability studies in the closed container in the aluminum pouch for up to at least 6 months. The Agency also stated the studies should include a continuous exposure open pouch vs intermittent exposure open pouch.

Aerie asked if there was any guidances or literature to refer to in regard to these stability recommendations. The Agency stated that they follow the ICH guidelines that provide evaluations of stability data; however, these guidances do not specify the in-use durations. The Agency recommended an additional 30 days.

b. Does the Agency agree that a suitable statistical analysis of stability data through (b) (4) could be used (b) (4) ?

FDA Response: No, while we agree statistical analysis may be used to support shelf life determination, we would not expect the projected extension to be more than one additional testing timepoint (i.e., 18 months). Note that the Phase 3 clinical trial container closure system (CCS) should represent the intended commercial CCS. Changes to the Phase 3 clinical trial CCS may require CMC bridging study and additional safety and efficacy studies.

Meeting Discussion: No further discussion was required.

c. Does the Agency agree that the Phase 3 batch "in-use" stability data could supplement and predict the in-use storage for the registration batch to justify in-use conditions?

FDA Response: The "in-use" evaluations at the 12, 24, and 36-month stability timepoints for one of each (b) (4) registration stability batches with the data should be provided in the NDA at time of submission rather than first NDA annual report. The studies may be done with aged sample study batches for a complete submission filing.

Meeting Discussion: Aerie asked the Agency if the proposed data package is acceptable for the proposed shelf life of 18 months and an in-use label. The Agency agreed that the data package proposed is acceptable to support an 18-month shelf life but referred to the earlier discussion concerning an in-use period.

d. If deemed necessary, would the Agency agree that Aerie could submit the 18-month timepoint and 12-month timepoint "in-use" stability data from the registration batch during the review period of the NDA application?

FDA Response: *No, we do not agree. The stability data information should be complete at submission. In general, we expect the NDA, at the time of submission to include 12 months long-term, and 6 months accelerated stability data for at least three registration batches, as recommended in ICH Q1A (R2). Alternatively, the "in-use" studies may be performed on aged storage samples for NDA inclusion.*

Meeting Discussion: Aerie stated that they would provide photostability data as well as freeze-thaw data as requested by the Agency. The Agency stated that if there is an agreed upon stability protocol and additional stability data meets the specifications described in that protocol, Aerie may propose extending the shelf life in the annual report.

NONCLINICAL

10. Does the Agency agree with Aerie's plan to initiate the proposed Phase 3 studies based on the two completed 3-month repeated-dose topical ocular toxicity studies in combination with the Phase 2 clinical study results, with the plan to have the 6-month repeated-dose topical ocular studies completed prior to Phase 3 studies going beyond 3 months of dosing?

FDA Response: *Yes, we agree, provided the 6-month animal study reports have been audited and contain signed pathology reports. We recommend that you plan your phase 3 study to allow adequate time (at least one month) for FDA review of the preclinical data prior to proceeding over 3 months in the clinic.*

Meeting Discussion: No further discussion was required.

11. Does the Agency agree that based upon data demonstrating that systemic exposure to AR-15512 following topical ocular administration is negligible and that AR-15512 is also generally recognized as safe as a flavoring agent or adjuvant used in or on human food products with no safety concerns; Aerie may request a waiver for carcinogenicity toxicology studies at the time of NDA submission?

FDA Response: *You may request a waiver of carcinogenicity studies at the NDA submission. The decision to grant a waiver is based on the review of the totality of the preclinical and clinical information received at the time of the waiver request.*

Meeting Discussion: No further discussion was required.

12. Does the Agency agree that no additional nonclinical data are needed to support Phase 3 and the eventual NDA?

FDA Response: *In support of your marketing application, we recommend that you perform embryofetal toxicity studies as per guidances ICHM3(R2)[1] and ICHS5(R3)[2]. You may provide waiver requests, along with justification and supporting data, for Fertility and Early Embryonic Development (FEED) as well as Pre/Postnatal Development (PPND) studies. Decision for waiver requests is generally made late in drug development, taking into consideration the totality of the preclinical and clinical information collected and submitted at the time of the waiver request. We recommend that you summarize all animal study toxicokinetic results and embryofetal development study results to support waiver requests for the FEED and PPND studies.*

While we don't anticipate the need for further general or ocular toxicity studies to support NDA submission, we cannot provide a final determination at this time. Such decisions are data-driven, and we have not reviewed all preclinical and clinical information yet.

As a general comment, all impurities and degradants that exceed guidance thresholds should be qualified at specified levels in the IND and NDA submissions.

[1]https://www.fda.gov/media/71542/download
[2]https://www.fda.gov/media/148475/download

Meeting Discussion: The Agency agreed with Aerie's proposals to use the two nonclinical species (rat and rabbit) to run the EFD studies. Aerie asked if receipt of the final EFD study reports from the rat and rabbit, as well as systemic plasma exposure data collected from the nonclinical and clinical safety program would be an acceptable data set to submit in support of the waiver for FEED/PPND study waivers. The Agency agreed with Aerie's proposal.

CLINICAL

13. The proposed Phase 3 safety and efficacy studies will be identical in design and conducted in approximately 450 DED subjects per study. Following a two-week run-in period on vehicle administered twice a day to both eyes, all eligible subjects will be randomized 1:1 to 0.003% AR-15512 or AR-15512 vehicle, which will be administered twice a day to both eyes for a period of (b) (4). All relevant details for the Phase 3 safety and efficacy studies can be found in the protocol synopsis (Appendix 1) .

a. Study Design: Does the Agency agree with the overall design of the proposed Phase 3 safety and efficacy studies?

FDA Response: *Agree. The overall design of the proposed Phase 3 safety and efficacy study is acceptable however, we recommend that the primary endpoints be collected on the same day or days that are close to one another.*

It is recommended that the clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. To accomplish this, it is

recommended that approximately 400 or more subjects using the AR-15512 ophthalmic solution complete treatment with a concentration at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. Prior to an NDA submission, it is recommended that safety data be available for at least 300 patients who have completed at least 3 months of follow-up after the initiation of treatment and at least 100 patients who have completed 12 months of follow-up after the initiation of treatment.

Meeting Discussion: Aerie acknowledged the Agency's feedback on the timing of the co-primary endpoints. Aerie asked the Agency if their revised proposal to measure the co-primary sign endpoint (proportion of subject with greater than 10 mm increase in unanesthetized Schirmer score) at Day 14 and (b) (4) was acceptable using a hierarchal statistical approach. The Agency agreed with the proposed plan.

b. Does the Agency agree that the key inclusion/exclusion criteria support the proposed indication of the treatment of signs and symptoms of dry eye?

FDA Response: Agree. The key inclusion/exclusion criteria are appropriate for studies of drugs proposed to treat the sign and symptom of dry eye.

Meeting Discussion: No further discussion was required.

14. For the Phase 3 safety and efficacy studies, Aerie proposes the following as co-primary efficacy endpoints where comparison is between 0.003% AR-15512 and AR-15512 vehicle:

- **The co-primary sign endpoint will be comparison of the mean change from baseline in unanesthetized Schirmer score**
- (b) (4)

a. Does the Agency agree that the proposed co-primary sign endpoint is appropriate and supports an NDA submission for the treatment of signs and symptoms of dry eye?

FDA Response: Agree. A co-primary sign endpoint of the change from baseline in unanesthetized Schirmer score at Day 14 (b) (4) *would be acceptable. A co-primary sign endpoint of the change from baseline in unanesthetized Schirmer score at Day* (b) (4) *would be acceptable. We do not recommend that the* (b) (4).

Meeting Discussion: No further discussion was required.

b. *Does the Agency agree that the proposed [redacted] endpoint is appropriate and supports an NDA submission for the treatment of signs and symptoms of dry eye?*

FDA Response: *See response to 14a.*

Meeting Discussion: No further discussion was required.

15. Aerie proposes the following timepoints for assessment of the co-primary efficacy endpoints:

- **The co-primary sign endpoint of comparison of the mean change from baseline in unanesthetized Schirmer score will be at Day 14**
- **[redacted]**

Does the Agency agree with the co-primary sign assessment timepoint being Day 14 [redacted]?

FDA Response: *See Response to 14a.*

Meeting Discussion: No further discussion was required.

16. Does the Agency agree that mean change from baseline in unanesthetized Schirmer score at either of these alternative timepoints ([redacted]), is appropriate and supports an NDA submission for the treatment of signs and symptoms of dry eye?

FDA Response: Mean change from baseline in unanesthetized Schirmer score [redacted] at either of these alternative timepoints (Day 14, [redacted]) would also be acceptable [redacted]

Meeting Discussion: No further discussion was required.

17. If so, does the Agency agree that any of the following alternatives listed below can be used as the co-primary sign endpoint?

a. Proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score at Day 14

FDA Response: Agree. Also, a statistically significant difference between the proportion of patients achieving a 10 mm increase or more in Schirmer scores can be used as an independent primary efficacy endpoint to demonstrate efficacy in treating dry eye.

Meeting Discussion: Aerie acknowledged the Agency's acceptance of the plan for the co-primary sign endpoint. Aerie asked for clarification regarding the Agency's comment in reference to the use of a Schirmer endpoint as an independent primary endpoint. The Agency clarified that a 10 mm increase in Schirmer score in each trial could be sufficient to demonstrate efficacy in treating dry eye.

b. Proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score (b) (4)

FDA Response: Agree. See response to question 17 a.

Meeting Discussion: No further discussion was required.

c. Proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score (b) (4)

FDA Response: Agree. See response to question 17 a.

Meeting Discussion: No further discussion was required.

18. Aerie may decide to modify the currently proposed (b) (4) **. If so, does the Agency agree that any one of the following alternatives listed below can be used** (b) (4) **?**

a. (b) (4)

FDA Response: Agree. Each of the alternative (b) (4) *endpoints and time points in questions 18 a -18 d are all acceptable.* (b) (4) *would each be acceptable provided that it is measured at approximately the same time as the sign endpoint.*

Meeting Discussion: No further discussion was required.

b. Mean change from baseline in (b) (4)

FDA Response: See 18a.

Meeting Discussion: No further discussion was required.

c. Mean change from baseline in (b) (4)

FDA Response: See 18a.

Meeting Discussion: No further discussion was required.

d. Mean change from baseline in [redacted] (b) (4)

FDA Response: See 18a.

Meeting Discussion: No further discussion was required.

19. Analysis of primary efficacy will be based on ANCOVA for both change from baseline endpoints. Available data only will be used if the discontinuation rate is < 5%; otherwise, an estimand based on multiple imputation will be used for the primary analysis. The co-primary endpoints will each be tested at the α=0.05 level using hierarchical, fixed sequence testing. The second endpoint in the hierarchy will only be tested if the first endpoint is significant at the α=0.05 level. Hence, no multiplicity adjustment is required.

a. Does the Agency agree with the proposed statistical strategy for the primary efficacy analysis for the Phase 3 safety and efficacy studies?

FDA Response: In the protocol synopsis, you have not clearly defined the primary estimand of interest to address the primary efficacy objective of the study. Noting that the primary estimand of interest should be aligned to the primary efficacy objective of the study, we cannot comment on the proposed primary efficacy analysis strategy at this stage of the IND. Additional comments may be provided when the full protocol including the statistical analysis section is submitted in the IND. In the statistical analysis section of the protocol, you should clearly define the primary estimand(s) of interest including strategy(ies) to handle intercurrent and missing data. Additionally, in the full protocol, you should specify the analysis populations and the statistical method (s) for the analysis of the co-primary and secondary efficacy endpoints by specifying the covariates to be included in the ANCOVA model.

To assess the robustness of the primary efficacy analysis results, you should describe potential sensitivity/supporting analyses in the full protocol and statistical analysis plan.

In the sample size calculation, you assumed a dropout rate of 10%. You should make every effort to minimize missing data and encourage subjects who discontinue the study due to adverse event or lack of efficacy to remain in the study for safety and efficacy evaluation at the scheduled study visits.

Meeting Discussion: No further discussion was required.

b. Does the Agency agree that achieving statistical significance in both pre-specified primary endpoints in both Phase 3 safety and efficacy studies will

be sufficient to support an NDA submission for the treatment of the signs and symptoms of dry eye?

FDA Response: *Agree provided that they are measured at approximately the same time.*

Meeting Discussion: No further discussion was required.

20. **As noted in Question 17, Aerie may elect to use proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score as the primary sign endpoint. Does the Agency agree that achieving as the first analysis, statistical significance in only this co-primary sign endpoint in both Phase 3 safety and efficacy studies would be sufficient to support an NDA submission for the indication of (b) (4) in patients with dry eye?**

FDA Response: *Yes.*

Meeting Discussion: No further discussion was required.

21. **Aerie is proposing the following as one of the secondary efficacy endpoints: "*mean change from baseline in quality of life* (b) (4) ." Does the Agency have any comments on the acceptability of this secondary endpoint?**

FDA Response: *In order to use this proposed patient reported outcome (PRO) tool for regulatory purposes, it should follow the Agency available Guidance Document, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"*

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

Meeting Discussion: No further discussion was required.

22. **Does the agency agree with the proposed statistical plan including multiplicity considerations for analysis of the secondary endpoints?**

FDA Response: *Please see Response to Question 19.*

Meeting Discussion: No further discussion was required.

23. **Does the Agency agree that the proposed LTSS is appropriate and sufficient to assess the long-term safety of AR-15512 in support of an NDA submission for the treatment of signs and symptoms of dry eye**?

FDA Response: *No. Though the long-term safety study design is acceptable, the protocols will not complete at least 300 patients who will be evaluated 3 months post treatment onset. Refer to the response to question 13a.*

Meeting Discussion: Aerie asked for clarification regarding the exposure calculation requirements provided by the Agency. Specifically, based on Aerie's proposed study enrollment targets and anticipated drop-out rates, Aerie anticipates that the number of patients exposed to the intended commercial formulation should be sufficient to meet the Agency's requirements for long term safety. The Agency stated that (b) (4) is not the same as 3 months (90 days) and recommended that the efficacy studies provide data for at least 300 patients who are evaluated for 3 months post-treatment . Aerie agreed to amend the phase 3 protocol to evaluate patients for 90-days.

24. Does the Agency agree that the proposed pharmacokinetic evaluation is sufficient to support an NDA submission for the treatment of the signs and symptoms of dry eye?

FDA Response: *No, we do not agree. The proposed pharmacokinetic (PK) sampling time points in Study AR-15512-LTSS are not adequate to characterize the pharmacokinetics of AR-15512 in humans. We recommend that you add additional PK sampling time points following the first dose and multiple dose to adequately assess the PK profile of AR-15512 in the proposed study. Also, note that the product you plan to administer in this clinical study should be the final To-Be-Marketed product to adequately characterize the PK for AR-15512.*

Meeting Discussion: Aerie stated that they have revised the plan for pharmacokinetics based on the Agency's feedback. Aerie proposed to add five PK sampling timepoints post dose. Specifically, Aerie proposed to collect a single pre-dose and 5 post dose blood samples (15 min, 30 min, 1 hr, 4 hr, 8 hr) at Day 1 (first dose) and after repeat dosing at Day 14 and Month 3. The Agency agreed that this revised proposal was acceptable. The Agency asked Aerie if the half-life is known from the pre-clinical samples so that one time point can be selected (either Day 14 or Month 3) for the multiple dose assessment instead of the two time points. Aerie will review the pre-clinical data to determine if Day 14 data will be adequate to characterize the PK of AR-15512 in humans following multiple doses. Aerie will provide a justification for this in the protocol.

25. Does the Agency agree that the planned extent of exposure to 0.003% AR-15512 is sufficient to support an eventual NDA for the treatment of signs and symptoms of DED?

FDA Response: *No. See Response to Question 13a and Question 23.*

Meeting Discussion: Aerie agreed with the Agency's recommendation to amend the Phase 3 protocols to reflect 90 days of safety data.

26. As the safety and efficacy studies will be completed prior to the completion of the LTSS, would the FDA accept an NDA submission that includes 6 months of interim safety data with the remainder of the 12 months of safety data provided as part of the 120-day Safety Update?

FDA Response: *Yes*

Meeting Discussion: No further discussion was required.

ADDITIONAL COMMENTS:

Combination Product Comments:

1) In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product. See 21 CFR Part 3. Should you disagree with the assessment that your proposed product is a combination product, you may contact the Office of Combination Products (OCP) at combination@fda.gov

2) Regarding eCTD location of combination product information, 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" December 2019 accessible at:

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf

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

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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

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 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]

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download
[8] https://www.fda.gov/media/85061/download

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.

ATTACHMENTS AND HANDOUTS

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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