CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217225Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 77902
Request Receipt Date	September 21, 2022
Product	Avacincaptad pegol
Indication	Treatment of geographic atrophy secondary to age-related macular degeneration
Drug Class/Mechanism of Action	Complement inhibitor
Sponsor	Iveric bio, Inc.
ODE/Division	OSM/DO
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	November 20, 2022

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Treatment of patients with geographic atrophy secondary to age-related macular degeneration

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

   ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO

   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Avacincaptad pegol is an inhibitor of complement activation that acts by binding complement C5. The mechanism of action of the drug product has not been established. The complement pathway and C5 are

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

theorized to be important mediators of inflammation in AMD.

GA secondary to AMD is a serious medical condition with both health and social impacts for patients. GA is an advanced form of AMD and is characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and choriocapillaris that leads to progressive and irreversible loss of visual function. No therapy is currently available for the treatment of GA.

8. **Information related to endpoints used in the available clinical data:**

For Study OPH2003, the primary efficacy endpoint was mean change in geographic atrophy area from baseline to Month 12 measured by fundus autofluorescence (FAF) at Baseline, Month 6, and Month 12.

In a SPA for Study ISEE2008 submitted May 24, 2021, the Agency and sponsor agreed to the following primary efficacy endpoint:

> Primary (Efficacy): Mean rate of change (slope) in geographic atrophy area over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12 (square root transformation)

To determine efficacy, the Division will apply the primary efficacy endpoint, the best polynominal fit mean rate of change in geographic atrophy over at least 12 months measured by fundus autofluorescence (FAF) at three time points.

9. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

There are no approved therapies to treat this condition. NDA 217171 (Pegcetacoplan ophthalmic solution) is currently under review in DO for the same indication.

10. **A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].**

Syfovre (pegcetacoplan intravitreal injection) is being studied for the same indication. Early in the development of Syfovre there was a request for breakthrough therapy designation which was denied (b) (4)

11. **Information related to the preliminary clinical evidence:**

The BTDR submission includes the sponsor's preliminary analyses of data from two adequate and well-controlled trials (Studies OPH2003 and ISEE2008) that the Sponsor plans to use in support of a future NDA submission.

Study ISEE2008 - See Table below

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Table 7: ISEE2008 Mean Rate of Change in GA from Baseline to Month 12 (MMRM Analysis; Square Root Transformation), Study Eye

	Avacincaptad pegol 2 mg N=225	Sham N=222
Square root area of GA (mm) at Baseline		
Mean	2.641	2.707
Standard Deviation	0.7142	0.6961
Median	2.521	2.653
Q1;Q3	2.028; 3.117	2.143; 3.212
Range	1.50; 4.19	1.53; 4.15
n	225	222
Square root area of GA (mm) at Month 12		
Mean	2.991	3.112
Standard Deviation	0.7205	0.7108
Median	2.860	3.064
Q1;Q3	2.423; 3.483	2.589; 3.662
Range	1.65; 4.65	1.79; 4.65
n	181	186
MMRM Analysis[b] - Rate of change from Baseline to Month 12		
Least Squares Mean (Growth Rate)	0.336	0.392
Standard Error	0.032	0.033
Difference[c]	--	0.056
% Difference[d]	--	14.25
95% CI	--	0.016; 0.096
p-value	--	0.0064

CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat population; MMRM = model for repeated measures; SAP = statistical analysis plan; VA = visual acuity

[b]MMRM is specified in the SAP, ISEE2008

[c]Difference in least squares means between groups calculated as (Sham) minus (avacincaptad pegol)).

[d]% Difference is calculated by 100*(Difference)/(Least Squares Mean from Sham).

Study ISEE2008 demonstrates a statistically significant reduction in the mean rate of GA area growth (slope) from Baseline to Month 12 between 2 mg avacincaptad pegol and sham (p-value = 0.0064) based on a growth rate determined from two timepoints (Baseline and Month 12). An analysis the rate of growth (slope) derived from three timepoints (Baseline, Month 6, and Month 12) was not presented in the BTDR.

Post-Hoc Slope Analysis of Primary Endpoint in Study OPH2003

The primary endpoint in Study ISEE2008 was slightly different than study OPH2003 and defined as:

- **The mean rate of growth (slope) estimated based on GA area measured in at least 3 time points.**

The primary efficacy endpoint in study ISEE2008 assumes a constant rate of growth over the evaluation period. To allow comparison of primary efficacy results across the pivotal studies, a post-hoc analysis (slope) of study OPH2003 was conducted, using the same primary analysis defined for study ISEE2008.

The post-hoc slope analysis of study OPH2003 showed a treatment effect of avacincaptad pegol 2 mg, with a difference of 27.73% (absolute growth rate difference: 0.109, descriptive p value = 0.0063; 95% CI 0.031; 0.186). Overall, the results were consistent with the prespecified primary efficacy results, supporting the beneficial treatment effects of avacincaptad pegol in the treatment of GA.

Only summary information of this post-hoc analysis was included in the BTDR. The analysis of the rate of growth (slope) derived from three timepoints (Baseline, Month 6, and Month 12) should be used to establish efficacy.

Systemic safety: Preliminary data have not identified any notable adverse events after 12-18 months of treatment.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: **Two randomized, double-masked, adequate and well controlled studies (i.e., OPH2003 [GATHER1] and ISEE2008 [GATHER2]) demonstrate statistical superiority, through a substantial reduction in the area of geographic atrophy, after one-year of treatment.**

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐DENY:

Provide brief summary of rationale for denial:

13. Division's next steps and sponsor's plan for future development:

The recommended analyses identified in Section 11 for Studies OPH2003 and ISEE2008, i.e., the mean rate of growth (slope) estimated based on GA area measured in at least 3 time points, should be included in the application to establish efficacy.

14. List references, if any: **N/A**

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐ NO ☒

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: Lucious Lim {See appended electronic signature page}
Team Leader Signature: Jennifer Harris {See appended electronic signature page}
Division Director Signature: Wiley Chambers {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

LUCIOUS LIM
11/17/2022 08:45:51 AM

JENNIFER D HARRIS
11/17/2022 08:51:07 AM

WILEY A CHAMBERS
11/17/2022 09:15:22 AM

IND 77902

MEETING MINUTES

IVERIC bio, Inc.
Attention: Luke Zack, PharmD, RPh
Associate Director, Global Regulatory Leader
1249 South River Road
Suite 107
Cranbury, NJ 08512

Dear Dr. Zack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Avacincaptad Pegol (ARC1905) solution for intravitreal injection. We also refer to the Type-B, Pre-NDA teleconference between representatives of your firm and the FDA on May 27, 2022.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, please contact Michael Puglisi, Regulatory Project Manager, at michael.puglisi@fda.hhs.gov or at (301) 796-0791.

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

MEMORANDUM OF MEETING MINUTES

Meeting Type/Category: Type-B, Pre-NDA

Meeting Date and Time: May 27, 2022, 9:00–10:00 am (Eastern)

Meeting Location: Teleconference

Application Number: IND 77902

Product Name: Avacincaptad Pegol (ARC1905) Solution for Intravitreal Injection

Indication: For treatment of Geographic Atrophy Secondary to Age-Related Macular Degeneration

Sponsor Name: IVERIC bio, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

Meeting Chair: Wiley Chambers
Meeting Recorder: Michael Puglisi

FDA PARTICIPANTS:

Charles Ganley, MD	Director, OND/Office of Specialty Medicine (OSM)
Alex Gorovets, MD	Deputy Director, OND/OSM
Wiley Chambers, MD	Director, Division of Ophthalmology/ Office of Specialty Medicine (DO/OSM)
William Boyd, MD	Deputy Director, DO/OSM
Jennifer Harris, MD	Clinical Team Leader, DO/OSM
Lucious Lim, MD	Clinical Reviewer, DO/OSM
David Summer, MD	Clinical Reviewer, DO/OSM
Martin Nevitt, MD	Clinical Reviewer, DO/OSM
Shilpa Rose, MD	Clinical Reviewer, DO/OSM
Greg Soon, PhD	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Abel Eshete, PhD	Statistical Reviewer, OB/DBIV
Ping Ji, PhD	Acting Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)
Amit Somani, PhD	Clinical Pharmacology Reviewer, OCP/DIIP
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
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 Sloan, PhD	Senior, Product Quality Reviewer, OPQ)/ONDP/ NDPB 6
Michael Puglisi	Senior Regulatory Project Manager, ORO/DROSM

SPONSOR PARTICIPANTS:

IVERIC bio, Inc.

Luke Zack, PharmD, RPh	Director, Global Regulatory Leader
Snehal Shah, PharmD	Chief Regulatory Strategy and Safety
Dhaval Desai, PharmD	SVP, Chief Development Officer
Kaitlyn Orland, PharmD, RPh	Senior Manager, Regulatory Affairs
Pravin Dugel, MD	President
Julie Yoon, PharmD	Senior Director, Safety Science Leader
Keith Westby, MS, MBA	SVP, Chief Operating Officer
Xiao-Ping Dai, PhD	SVP, Chief Technical Officer
Julie Clark, MD, MS	Vice President, Clinical Development
Will Schubert, PhD	Director, Preclinical Development
Justin Tang, PhD	Senior Director, Biostatistics
Liansheng Zhu, PhD	VP, Head of Biostatistics
Xiao-Ping Dai, PhD	SVP, Chief Technical Officer
Karen Xu, PhD	Senior Director, Regulatory Affairs CMC
Zach Zhu, PhD	Senior Director, DP Development and Manufacturing
Radha Iyer	SVP, Quality Assurance

(b) (4) Consultant

MEETING OBJECTIVE:

The Sponsor requested this meeting to discuss the planned submission of the NDA application for Avacincaptad Pegol (ARC1905) solution for intravitreal injection for treatment of Geographic Atrophy Secondary to Age-Related Macular Degeneration.

SUMMARY OF DISCUSSION:

Agency preliminary responses (see text in italics below) to the question outlined in the April 20, 2022, background package (see bolded text below) were provided to the Sponsor in an email dated May 19, 2022. This meeting served to clarify the Agency responses. Discussion during the meeting is reflected in regular font.

QUESTIONS FOR THE AGENCY:

Content and Format Questions

1. **Integrated Efficacy**
   Data from adequate, and well-controlled Studies OPH2003 (GATHER1) and ISEE2008 (GATHER2), which will be provided in individual clinical study reports (CSRs), the Summary of Clinical Efficacy (SCE), and the Integrated Summary of Effectiveness (ISE), will establish the efficacy of avacincaptad pegol in the treatment of patients with GA.

   Does the Agency agree with the Sponsor's approach to providing efficacy data, including content and analyses, to support the planned NDA submission?

   Agency Response: The Agency has no objection to your approach to present efficacy data to support the planned NDA. Please provide datasets and clinical study reports for each individual study separately.

   Meeting Comment: There was no discussion of this matter during the meeting.

2. **Integrated Safety**
   Data from completed and ongoing studies, which will be provided in individual CSRs, the Summary of Clinical Safety, and the Integrated Summary of Safety (ISS), will establish the safety of avacincaptad pegol in the treatment of patients with GA. These data will cover all avacincaptad pegol clinical studies, including patients with GA and other ocular indications (i.e., neovascular AMD [nAMD], idiopathic polypoidal choroidal vasculopathy [IPCV] and Stargardt Disease).

   a) **Does the Agency agree with the Sponsor's approach to providing safety data, including content and analyses, to support the planned NDA submission?**

      Agency Response: The Agency has no objection to your approach to present safety data to support the planned NDA.

   b) **Does the Agency agree with the Sponsor's approach to evaluate Treatment-Emergent Adverse Events (TEAE) of interest?**

      Agency Response: The Agency has no objection to your approach to evaluate TEAE of interest. However, we recommend that all TEAE be evaluated including TEAE of interest.

   Meeting Comment: There was no discussion of the Agency preliminary responses to Question 2 during the meeting.

3. **4-Month Safety Update**
   The Sponsor intends to provide a 4-month safety update (4-MSU) that includes masked-data listings and summaries, similar to what is provided in the Drug Safety Update Report (DSUR), from all ongoing avacincaptad pegol clinical trials (e.g., OPH2005, ISEE2008 >12 months, and any other recently commenced clinical trials) with a clinical cut-off date that is at least 2 months prior to the intended 4-MSU submission date. Does the Agency agree with the proposed approach?

   Agency Response: The Agency has no objection to your approach on submission of the 4-month safety update.

   Meeting Comment: There was no discussion of this matter during the meeting.

4. **Clinical Pharmacology Summary**
   Does the Agency agree with the Sponsor's approach to the content and format of Module 2.7.2, Summary of Clinical Pharmacology Studies?

   Agency Response: Overall, the plan appears reasonable. However, we recommend you clarify the location for the pharmacokinetic (PK) study report in the NDA from Clinical Study ISEE2008 that you mention in Table 7 on page 349 of your meeting package and whether it will be a standalone study report or part of the ISEE2008 clinical study report.

   Meeting Discussion: The Sponsor clarified that a separate, standalone ISEE2008 PK study report (i.e., not part of the CSR) would be provided in Module 5.3.3.2. The Sponsor also stated that the ISEE2008 CSR would be provided in Module 5.3.5.1. The Agency agreed with the proposed approach.

5. **Case Report Forms and Patient Narratives**
   The Sponsor proposes to include case report forms (CRFs) and patient narratives for deaths, adverse events leading to discontinuations, related and unrelated serious adverse events (SAEs) for all Phase 1, 2, and 3 studies in the new drug application (NDA) package. Does the Agency agree with this approach?

   Agency Response: The Agency has no objection to your approach to submit CRFs and patient narratives.

   Meeting Comment: There was no discussion of this matter during the meeting.

6. **Benefit Risk Evaluation and Patient Experience Data**
   a) **The Sponsor will provide an integrated summary of the benefits and risks of avacincaptad pegol for the proposed indication in the Clinical Overview in Module 2.5. Does the Agency agree with this approach?**

Agency Response: *The Agency has no objection to this approach.*

b) **Patient experience data derived from the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25, VFQ-25) will be included in the NDA as part of the individual CSRs. Additionally, separate patient-reported outcome (PRO) reports for the GATHER1 and GATHER2 clinical trials are planned to be included to support patient reported responder analyses and interpretation of change from baseline on the VFQ-25 domains by using methods consistent with Patient-Focused Drug Development (PFDD) Guidance for Clinical Outcome Assessments (COA). The relevance of this information, in context of benefit-risk, will be summarized in the Clinical Overview. Does the Agency agree with this approach?**

Agency Response: *The VFQ-25 is not a validated PRO.*

Meeting Comment: There was no discussion of the Agency preliminary responses to Question 6 during the meeting.

7. **Study Data Standardization Plan, Datasets, and Programs**
Clinical data in the proposed NDA submission will be provided, as described in Appendix 13, in compliance with the Clinical Data Interchange Standards Consortium (CDISC) standards. Does the Agency agree with the Sponsor's proposed data package for the NDA submission?

Agency Response: *Acceptable.*

Meeting Comment: There was no discussion of this matter during the meeting.

8. **Bioresearch Monitoring**
Does the Agency agree with the Sponsor's proposal on the submission of Summary Level Clinical Site Data to the Office of Scientific Investigation to meet bioresearch monitoring (BIMO) requirements and support the Agency's inspection of clinical sites?

Agency Response: *The Agency has no objection to your proposal to meet bioresearch monitoring requirements.*

Meeting Comment: There was no discussion of this matter during the meeting.

Administrative/ Regulatory Questions

9. **Clinical Summaries and Integrated Analyses Location Within eCTD The Sponsor proposes the 2.7.3 Summary of Clinical Efficacy, and 2.7.4 Summary of Clinical Safety would be sufficiently detailed to serve as**

the narrative portion of the ISS and ISE, respectively, while still concise enough to meet the suggested size limitations for Module 2 (<400 pages). The ISE and ISS appendices comprising tables, listings, figures, and datasets will be located in Module 5.3.5.3. Does the Agency agree with this approach?

Agency Response: The Agency has no objection to this approach.

Meeting Comment: There was no discussion of this matter during the meeting.

10. **Financial Disclosure**
Does the Agency agree with the Sponsor's proposed list of studies for which clinical investigator financial disclosures will be provided?

Agency Response: The Agency has no objection to the proposed list of studies that you will provide clinical investigator financial disclosures.

Meeting Comment: There was no discussion of this matter during the meeting.

11. **Combination Product Qualification**
The Sponsor is considering co-packaging components, such as a transfer filter needle, injection needle, and empty syringe, with the DP vial.

a) **Can the Agency confirm that this proposed commercial presentation would constitute and be regulated as a combination product?**

Agency Response: Yes. The proposed commercial presentation would constitute and be regulated as a combination product.

b) **If designated a combination product, does the Agency agree that the Sponsor's proposed documentation is adequate to support the NDA?**

Agency Response: No. The Agency expects at least one of the clinical trials use the to-be-marketed product.

In addition to the letters of authorizations for each of the co-packaged device constituent parts (which you indicate will be commercially available), your future NDA submission should address whether each co-packaged device constituent part is being used in accordance with its cleared labeling and whether it is being repackaged and/or resterilized.

We understand that you are planning to use avacincaptad pegol to treat geographic atrophy (GA) and that you propose to co-package the drug product vial with components such as transfer filter needle, injection needle, and empty syringe. However, you have not submitted a comprehensive risk analysis or your plans for a Human Factors (HF) validation study.

As a combination product we recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications. You may wish to refer to draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development[1].

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

Based on the aforementioned information and data, you should determine whether you need to submit the results of a human factors (HF) validation study with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that an HF validation study does not need to be submitted for your product, submit your risk analysis, comparative analyses, and justification for not submitting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents[2]:

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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] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

You may also wish to refer to three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[3]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

Meeting Discussion: The Sponsor clarified details of the to-be-marketed product, stating that the vial kit used in ongoing clinical study ISEE2008 includes the (b) (4) vial, an empty 1 mL Luer-Lok syringe, a 5-micron filter needle, and a 30-g ge injection needle (syringe, filter needle, and injection needle are all manufactured, packaged, and labeled by (b) (4) The Sponsor stated that the (b) (4) The syringe and filter needle would be provided as single, sterilized units with the appropriate cleared labeling and packaging from (b) (4) and therefore no repackaging or resterilization are needed. The Agency recommended that the Sponsor specify these details in the NDA submission.

The Sponsor confirmed they will conduct a comprehensive risk analysis as requested by the Agency and will submit the human factors engineering report to the IND for review.

The Sponsor explained that the risk analysis would include a use-related risk analysis (URRA) and task analysis that would define all critical and noncritical tasks for injection preparation and procedure, as described in the instructions for use (IFU). The Sponsor stated the URRA would evaluate the implications if use errors or task failures occurred and would consider relevant information from experience, literature, and other similar approved combination products.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The Sponsor stated that they also plan to implement a comparative analysis in the assessment that will analyze other similar marketed combination products. The Agency agreed the Sponsor's planned approach for human factors risk analysis sounds reasonable.

The Sponsor asked if there are specific risks they should be concerned with based on the Agency's experience with similar vial kits which are currently marketed. The Agency stated there are no specific issues with similar vial kits on the market and it is primarily interested in use errors and/or dosing errors which could lead to adverse events.

The Agency stated the human factors and risk analysis information should be included with the NDA at the time of submission. Items related to compliance for combination ophthalmology products can be provided up to 12 months after the effective date of the March 2022, guidance entitled "Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4."

12. **Overall NDA Format and Table of Contents**
Does the Agency agree that the overall proposed format and content of the NDA submission is adequate to support an NDA submission?

Agency Response: The Agency has no objection to the proposed overall NDA format and content.

Meeting Comment: There was no discussion of this matter during the meeting.

13. **Priority Review**
Avacincaptad pegol is a new potential treatment for GA, a serious condition with no approved therapies. Understanding that a request for Priority Review will be considered by the Agency at the time the application is submitted, does the Agency agree that a potential new drug for treatment of patients with GA is a candidate for Priority Review?

Agency Response: An NDA submitted for the indication treatment of GA may potentially qualify for priority review. The determination will be made after the filing of the application.

Meeting Comment: There was no discussion of this matter during the meeting.

14. **Advisory Committee Meeting**
Does the Agency anticipate convening an Advisory Committee meeting for a potential new drug for treatment of patients with GA?

Agency Response: It is premature to answer the question at this time. That determination will be made after the filing of the NDA.

Meeting Comment: There was no discussion of this matter during the meeting.

15. Other Feedback
Does the Agency have any additional points for the Sponsor's consideration regarding the planned NDA submission?

Agency Response: See below.

Additional Agency Comments:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION
As stated in our DATE communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan USE IF APPLICABLE FOR CONTROLLED SUBSTANCES: , as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.
https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

PRESCRIBING INFORMATION
In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development and Pregnancy and Lactation Labeling Final Rule https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development websites, which include:

- *The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.*
- *The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.*
- *·Regulations and related guidance documents.*
- *A sample tool illustrating the format for Highlights and Contents, and*

- *The Selected Requirements for Prescribing Information (SRPI)− a checklist of important format items from labeling regulations and guidances.*

- *FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.*

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

MANUFACTURING FACILITIES
To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	*Site Address*	*Federal Establishment Indicator (FEI) or Registration Number (CFN)*	*Drug Master File Number (if applicable)*	*Manufacturing Step(s) or Type of Testing [Establishment function]*
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	*Site Address*	*Onsite Contact (Person, Title)*	*Phone and Fax number*	*Email address*
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h https://www.fda.gov/media/84223/download and the guidance for industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers. https://www.fda.gov/media/84223/download
Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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. https://www.fda.gov/media/84223/download

Meeting Comment: There was no discussion of the Additional Agency Comments during the meeting.

ACTION ITEM:
The Agency agreed to provide minutes of the meeting within 30 days.

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/

WILEY A CHAMBERS
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