CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216675Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 130558

MEETING MINUTES

Bausch & Lomb Incorporated
Attention: Mary Harrell, BsBM, RAC
Senior Director, Global Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your Investigational New Drug Application (IND) file for NOV03 (perfluorohexyloctane ophthalmic solution). We also refer to the telecon between representatives of your firm and the FDA on December 15, 2021. The purpose of the meeting was to discuss filing of your new drug application (NDA).

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager at (301) 796-1002.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 15, 2021 from 12:30-1:30 PM EST
Meeting Location:	Teleconference
Application Number:	IND 130558
Product Name:	NOV03 (perfluorohexyloctane ophthalmic solution)
Indication:	Treatment of patients with Dry Eye Disease
Sponsor Name:	Bausch & Lomb, Incorporated
Regulatory Pathway:	505(b)(1)

FDA ATTENDEES

Wiley Chambers, MD	Director, Division of Ophthalmology (DO)
William Boyd, MD	Deputy Division Director, DO
Rhea Lloyd, MD	Clinical Team Leader, DO
Chunchun Zhang, PhD	Product Quality Team Leader, Office of Pharmaceutical Quality/Division of New Drug Products/New Drug Products Branch III
Milton Sloan, PhD	Product Quality Reviewer, OPQ/NDPB-III
Daniel Jansen, PhD	Product Quality Reviewer, OPQ//NDPB-III
Lori Kotch, PhD	Nonclinical Supervisor, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
Aling Dong, PhD	Nonclinical Reviewer, DPT-RPURM/SM
Suneet Shukla, PhD	Clinical Pharmacology Team Leader, OTS/OCP/DIIP
Hyewon Kim, PhD	Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Greg Soon, PhD	Statistics Team Leader, Office Biometrics/Division of Biometrics IV (OB/DBIV)
Solomon Chefo, PhD	Statistician, OB/DBIV
Jacquelyn Smith, MA	Senior, Regulatory Health Project Manager, ORO/DROSM

SPONSOR ATTENDEES

Mary Harrell, BsBM, RAC	Senior Director, Global Regulatory Affairs
Helen Liou, MS	Senior Manager, Global Regulatory Affairs
Christopher Uhrn	Director, Regulatory Affairs – CMC

Shankar Swaminathan	Executive Director, Regulatory Affairs – CMC
William Jo, PhD, DABT	Executive Director, Nonclinical R&D
Gene Williams, PhD	Vice President, Clinical Pharmacology and Pharmacokinetics, Nuventra, LLC
Johnson Varughese	Vice President, Clinical Services
Jason Vittitow, PhD	Executive Director, Clinical Affairs R&D
Dan Donatello	Assoc. Director, Clinical Trial Manager
Susan Harris	Senior Director, Biostatistics, R&D
Gary Mosehauer, MS	Director, Biostatistics, R&D
Jingshi Zhang, PhD	Assoc. Director, Clinical Pharmacology
Sarabjit Gahir	Director, Clinical Pharmacology

1.0 BACKGROUND

Bausch & Lomb requested a meeting to discuss filing of your new drug application (NDA). FDA provided preliminary comments to Bausch & Lomb's questions on December 8, 2021. After receipt of the preliminary responses, Bausch & Lomb provided responses prior to the meeting and requested discussion of questions 6 and 11. The questions are provided in **bold** font, the Agency's preliminary comments are provided in *italic* font, Bausch and Lomb's responses are provided in ***bold italic*** font and the discussion is provided in normal font.

2.0 DISCUSSION

NONCLINICAL QUESTIONS

Question 1:

The toxicity of perfluorohexyloctane was characterized in oral and topical ocular repeated dose, genotoxicity and oral embryofetal development toxicity studies. Additionally, nonclinical pharmacology and pharmacokinetic studies confirmed its limited tissue distribution and exposure.

Does the Agency agree that no additional nonclinical studies will be required for a 505(b)(1) NDA for NOV03 (perfluorohexyloctane) for the treatment of the signs and symptoms of DED?

FDA Response: We do not expect additional nonclinical studies at this time. However, adequacy of the data will be a review issue.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

Question 2:

The Applicant conducted rat and rabbit embryofetal development toxicity studies with oral administration of perfluorohexyloctane covering the entire organogenesis period. A number of fetal malformations were observed in rabbits following

perfluorohexyloctane treatment at maternal doses that exceeded the maximum tolerated dose but not in rats. The rabbit findings were likely secondary to the moderate to severe maternal toxicity which resulted in some abortions and/or early terminations, and do not represent a safety concern to DED patients; this is based on the inert nature of perfluorohexyloctane, the high safety margins to human systemic exposures, and lack of correlating findings in rats at even higher systemic exposures.

Does the Agency agree that no additional embryofetal development toxicity studies will be required for marketing authorization, and that the existing data from both species are adequate for informing pregnancy risks?

FDA Response: We do not expect to recommend additional embryofetal development toxicity studies for marketing authorization at this time. However, adequacy of the data will be a review issue.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

Question 3:
The Applicant intends to address in the NDA the DNA reactivity risk of chemicals identified in extraction and leaching studies conducted on the container closure system per recommendations in the ICH M7(R1) Guidance, "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk". Additionally, any chemical that exceeds the qualification threshold for ophthalmic products of 20 ppm will be qualified by toxicity database and literature information.

Does the Agency agree with our plan?

FDA Response: Your approach appears acceptable. A final decision as to the adequacy of the data to support approval will be a review issue.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

CLINICAL/PHARMACOLOGY/BIOSTATISTIC QUESTIONS

Clinical
Question 4:
During the End-of-Phase 2 (EOP2) meeting, the Agency considered the potential for the Phase 2 and pivotal Phase 3 acceptable for filing a new application seeking

approval for the intended indication. The totality of clinical efficacy data collected during the single Phase 2 (NVU-002), and first Phase 3 study (NVU-003), where BID and QID dosing of NOV03 were evaluated and shown to be statistically significant at the pre-specified primary and secondary endpoints, provides sufficient safety and efficacy data to support a dosing regimen of (b) (4) 4 times per day, as directed by the physician. A summary of the available clinical data and intended outcomes for the overall program are provided in the meeting materials.

a. **Does the Agency agree that the clinical program described adequately supports a substantiated Agency evaluation of efficacy and safety of the formulation for the proposed indication?**

FDA Response: Your question is not clear. Depending upon the results of the ongoing BL904 study, the clinical studies of NOV03 conducted should support filing of an NDA.

Bausch & Lomb Response: Acknowledge with no further comment

b. **Does the Agency agree with the rationale, supporting data, and dosing regimen selected for this program?**

FDA Response: It is acceptable.

Bausch & Lomb Response: Acknowledge with no further comment.

c. **Does the Agency agree, given the totality of clinical efficacy data (b) (4) support a dosing regimen of (b) (4) 4 times a day? If not, the applicant requests clarification on the necessary supplemental data to support this dosing regimen?**

FDA Response: Labeling is a review issue. This question cannot be adequately answered prior to a review of the new drug application. (b) (4) .

Bausch & Lomb Response: Acknowledge with no further comment

d. **Does the Agency agree with the overall safety population, evaluation and presentation adequately supports the new formulation in the claimed dosing regimen ((b) (4) 4 times a day)?**

FDA Response: Please describe any changes to the formulation of NOV03 during the clinical development program. It is unclear what could have changed since NOV03 is 100% perfluorohexyloctane. The overall safety population and safety database should be adequate

Bausch & Lomb Response: ***The Applicant acknowledges the Agency's comments and confirms no changes have been made to the formulation of NOV03 during the clinical development program.***

Meeting Discussion: None

Question 5:
Continuing the development plan by replicating the Phase 2 study design, the prespecified primary endpoint of signs and symptoms in the Phase 3 studies was measured at Day 57 and the prespecified secondary endpoint of sign and symptom was measured at Day 15. Statistically significant and clinically relevant treatment effects beginning at Day 15 and maintained through Day 57, will be presented in the NDA. Based on the plans to provide the totality of the safety and efficacy data, as described in the meeting materials, the applicant will provide substantial evidence that the product is safe and effective at Day 15 and Day 57.

Does the Agency agree with the Applicant's proposal for specifying treatment effect at Day 15 and Day 57? If not, we ask the Agency to provide recommendations for inclusion of clinically meaningful data (prespecified primary and secondary endpoints).

FDA Response: Labeling is a review issue. This question cannot be adequately answered prior to a review of the new drug application. An appropriate multiplicity adjustment that controlled the study-wise Type 1 error rate at two-sided significance level of 5% should be made to specify the treatment effect at Day 15 and Day 57.

Bausch & Lomb Response: ***Acknowledge with no further comment.***

Meeting Discussion: None

Clinical Pharmacology
Question 6:
Reference is made to the EOP2 meeting minutes and supporting reports included in the associated meeting materials (NVU-002 Clinical Trial Report Table 14.3.1.1 [Seq0014], NVU-002 Clinical Trial Report Table 16.2.5.3.1 [Seq0008], Bioanalytical Report [Seq0014], and Bioanalytical Report Amendment [Seq0017]), wherein the agency agreed that the available pharmacokinetic data were sufficient to support a marketing application.
After QID topical ocular administration of NOV03, blood concentrations of perfluorohexyloctane were measured in a subset of DED patients in the study. Following 57 days of instillation in 21 subjects, blood concentrations ranged from 0.00-25.50 ng/mL with a mean of 8.192 ng/mL Based on these data, the Applicant concludes that systemic concentrations of perfluorohexyloctane were low, consistent with the low drug absorption associated with the topical ocular route of

administration. No safety concerns are expected at these systemic exposure levels and safety margins from nonclinical toxicology data.

Does the Agency agree with the Applicant's conclusion and that no further pharmacokinetic evaluations are necessary to support the proposed formulation in the intended application?

FDA Response: Although we agree that your approach of clinical PK data analysis is reasonable to support a future marketing application, your bioanalytical method appears inadequate since several pre-dose or control (saline) group samples demonstrated measurable NOV03 concentrations and your incurred samples reanalysis did not meet the acceptance criteria. Considering this, your current clinical PK data cannot be used for labeling purpose. To include PK data in the labeling, you need to redevelop the bioanalytical method and re-analyze clinical samples with acceptable in-study bioanalysis results.

Bausch & Lomb Response: We acknowledge the Agency comments indicating that the approach of the PK data analysis of Study NVU-002 is reasonable to support the planned marketing application but cannot be used for labeling purpose. We plan to include a clinical pharmacology summary in the label for perfluorohexyloctane to satisfy the labeling requirements. Is this planned approach reasonable to the Agency?

Meeting Discussion: Bausch & Lomb asked the Agency for comments. The Agency stated that they would review any submitted language in the context of the review of the entire application. A clinical pharmacology summary is not a requirement if it is not relevant to the safety. The sponsor acknowledged the Agency's response and needed no further clarification.

Biostatistics
Question 7:
Approximately 944 human subjects will have been exposed to at least 1 dose of NOV03 as part of the development program, including approximately 840 subjects exposed to NOV03 in the 8-week Phase 2 and Phase 3 studies. A total of 209 subjects have been enrolled in NVU-004 with approximately 105 subjects receiving NOV03 for the first time.

Does the Agency agree that the total subject exposure is adequate to satisfy the NDA filing requirement?

FDA Response: Agree.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

Question 8:
The summaries of NVU-004 to be included in the initial NDA submission for filing will include at least 100 subjects treated with NOV03 QID who have reached at least the 6-month visit (Visit 4, Week 26). A total of approximately 150 subjects will have completed Week 52 visit (Visit 6) in the study during the planned NDA review. Available data from all scheduled visits will be summarized including visits later than the 6-month visit. The final clinical study report and all associated data will be submitted with the 120-day safety update.

Does the Agency agree that the overall plans for the interim analysis and final study report for study NVU-004 and will be acceptable for the initial NDA filing and 120-day safety update, respectively?

FDA Response: The final clinical study report needs to be submitted with the original application.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

Question 9:
Statistical analysis of the safety data for the pivotal Phase 3 studies NVU-003 and BL904 conducted with the to-be-marketed formulation will be pooled by treatment group and presented as an Integrated Summary of Safety (ISS) section in Module 2. For the ISS, the Sponsor plans to summarize subject disposition, medical history, and concomitant medications for the Safety Population by treatment for the pooled Phase 3 pivotal studies NVU-003 and 904. In addition, the following will be summarized for the Safety Population by treatment group: treatment exposure, treatment compliance, treatment-emergent adverse events, visual acuity, slit-lamp biomicroscopy, intraocular pressure, and dilated fundoscopy. Ocular adverse events will be summarized by Age Group (<65 years, >=65 years), by Sex, and by Race (White, Non-White), and by baseline dryness score VAS (<70 vs ≥ 70). Safety data from the Phase 2 study (NVU-002) and open-label extension study (NVU-004) will be summarized and described separately in Module 2. Safety data from post-marketing studies NT-001 through NT-004 will similarly be summarized and described separately. The appendices and datasets to support the analyses will be provided in Module 5.

Does the Agency agree with the statistical analysis plan for pooling of safety data for the Phase 3 clinical studies?

FDA Response: Please describe any changes to the formulation of NOV03 during the clinical development program. It is unclear what could have changed since NOV03 is 100% perfluorohexyloctane.

A presentation of the pooled safety data based on dosing regimen of NOV03 compared to placebo throughout the clinical development program in the Integrated Summary of Safety would also be helpful.

Safety should be summarized and described separately for all individual studies. As supporting analysis, we have no objection to your proposed plan for pooling of safety data for the Phase 3 clinical studies.

Bausch & Lomb Response: The Applicant acknowledges the Agency's comments and confirms no changes have been made to the formulation of NOV03 during the clinical development program.

Meeting Discussion: None

Question 10:
Statistical analysis of the efficacy data for the pivotal Phase 3 studies NVU-003 and BL904 conducted with the to-be-marketed formulation will be pooled by treatment group and presented as an Integrated Summary of Efficacy (ISE) section in Module 2. For the ISE, the Sponsor plans to summarize and compare QID dosing of NOV03 vs. Saline for the primary and secondary endpoints of the pooled pivotal Phase 3 trials NVU-003 and BL904. These comparisons will be made for the ITT Population, by Age Group (<65 years, >=65 years), by Sex, Race (White, Non-White), and by baseline dryness score VAS (<70 vs ≥ 70). Efficacy data from the Phase 2 study (NVU-002) and open-label extension study (NVU-004) will be summarized and described separately in Module 2. Efficacy data from post-marketing studies NT-001 through NT-004 will similarly be summarized and described separately. The appendices and datasets to support the analyses will be provided in Module 5. A summary of the statistical analysis plans is provided in the meeting materials.

Does the Agency agree with the statistical analysis plan for pooling of efficacy data for the Phase 3 clinical studies?

FDA Response: Efficacy should be described separately for each individual study. As supporting analysis, we have no objection to your proposed plan for pooling of efficacy data for the Phase 3 clinical studies.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

QUALITY (CHEMISTRY-MANUFACTURING-CONTROLS) QUESTIONS

Question 11:

[redacted] **The drug substance route of synthesis, starting material route of synthesis and starting material specifications are provided in the meeting materials.**

Based on the information presented, does the Agency concur with the Applicant's approach for identification of [redacted] **as the starting materials for synthesis of Perfluorohexyloctane?**

FDA Response: You did not include sufficient information to justify your proposal. The following additional information should be provided in the NDA:

- *Information to support the claim that the proposed compound is a commercially available chemical (i.e., sold as a commodity in a preexisting, non-pharmaceutical market).*
- *Specification to include identity, purity, specified, unspecified, and total impurities.*
- *Justification for impurity limits, with data from 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).*
- *Upstream synthesis (including all the materials, reagents, solvents, and catalysts used in the synthesis) and assessment of the final steps for potential mutagenic impurities.*
- *Assessment of the potential and actual impurities and fate/purge data for such impurities and their derivatives in the manufacturing process of the drug substance.*
- *Batch analysis data from several batches showing material of consistent quality and acceptable impurity levels*

Bausch & Lomb Response: Bausch acknowledges the Agency's response to Question #11 and the requested information will be provided in the NDA. Regarding information to support our claim that the starting materials are commercially

available, Bausch would like to provide the below list of suppliers for the starting materials. Additionally, the annual tonnage of (b) (4) ***is in excess of*** (b) (4) ***pounds.***

(b) (4)

a. Is this information sufficient to support the commercial availability of the starting materials?

Meeting Discussion: The Agency responded that the information the sponsor provided above is expected to be sufficient to support the commercial availability of the starting materials.

Bausch would also like to clarify that the 109 identified structures mentioned in Question #14 are comprised of starting materials, reagents, catalysts and solvents, including their actual impurities and potential synthetic structures of known class of impurities, the intermediates and "potential synthetic impurities" that could arise during the synthesis of the drug substance due to possible reactions in between species present at each step of the manufacturing process.

b. Is this approach adequate to support the additional information requested by the Agency to identify (b) (4) ***as the starting materials?***

Meeting Discussion: The Agency responded that the approach the sponsor proposed above is expected to be supportive of establishing the starting materials.

Question 12

[redacted], the drug substance manufacturer has manufactured three process validation batches at their building designated as [redacted] (theoretical scale of [redacted] kg). Batches from [redacted] were used to manufacture the registration and Phase 3 Clinical batches. An additional building, [redacted] located within the same contiguous campus will be utilized to manufacture the drug substance at a larger scale for commercial purposes. To date, [redacted] has manufactured one validation batch at a theoretical scale of [redacted] kg at [redacted]. Comparisons of the manufacturing process parameters, in-process controls, manufacturing equipment, manufacturing processes, comparative flow diagrams, and comparative batch release data are provided in the meeting materials. The Applicant plans to utilize drug substance from both [redacted] for commercial drug product batches.

Based on the information provided does the Agency agree with Applicant's plan to utilize drug substance manufactured at [redacted] for commercial purposes?

FDA Response: We agree with your plan to utilize the drug substance manufactured at [redacted] for commercial purposes. Include in the NDA: All comparative information included in this meeting briefing package and 3-month of long-term and accelerated stability data for at least 1 batch of drug substance manufactured at [redacted].

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

Question 13

The Applicant plans to remove testing of [redacted] residual solvents from the drug substance specifications based on data from several drug substance batches, which demonstrate levels well below the control limit. In addition, the Applicant plans to remove testing of [redacted] from the drug substance specifications based on data from several batches, which demonstrate levels well below the control limit. The Applicant plans to continue to test for [redacted], which is used as a solvent in the synthesis with a limit of NMT [redacted] ppm and for [redacted], which is used as a catalyst in the synthesis with a limit of NMT [redacted] ppm. Residual Solvent and elemental impurity data are provided in the meeting materials.

Does the Agency concur with the Applicant's plan to remove testing of [redacted] residual solvents and elemental impurities [redacted]?

FDA Response: Your plan to remove [redacted] residual solvents and the elemental impurities [redacted] from the drug substance

specification is acceptable. We remind you that ICH Q3D "Elemental Impurities" and USP <232>/<233> apply to the finished drug product and the assessment of elemental impurities that may arise from the synthesis (e.g., catalysts), processing equipment, container/closure systems, and components (e.g., excipients) of the drug product. A risk assessment should be conducted, and the summary report should be submitted in P.2 section of your NDA as per FDA's guidance "Elemental Impurities in Drug Products Guidance for Industry".

***Bausch & Lomb Response:* Acknowledge with no further comment**

Meeting Discussion: None

Question 14
An ICH M7 compliant toxicological analysis on 109 structures was performed and a total of eight structures were categorized as (b) (4) potential mutagenic impurities. The complete assessment of potential mutagenic impurities was presented in Section 3.2.S.3.2 of the IND and will be provided in the NDA.
The scientific risk assessment, developed by the use of substantial worst case scenarios and very safe purge factors, demonstrates the capability of the process to significantly reduce all eight (b) (4) potential mutagenic impurities at a total level that is significantly below the calculated acceptable limits for the drug product at the target dosage of 120 mg/day and duration treatment of >10 years to lifetime. Consequently, the risk that the cumulative concentration ((b) (4) ppm) of these impurities could potentially be above this limit, in the drug substance and drug product is negligible. Therefore, analytical testing to control these impurities at release is not necessary. Further details of the Applicant's method of assessment performed by the adoption of option 4 of ICH M7 guidance are found in the meeting materials.

Does the Agency agree with the application of ICH M7, option (b) (4) for the control strategy of potential (b) (4) mutagenic impurities and our conclusion that controlling these impurities at release is not necessary?

FDA Response: We agree with application of ICH M7, option (b) (4) as the control strategy for potential (b) (4) mutagenic impurities and controlling these impurities at release is not necessary.

***Bausch & Lomb Response:* Acknowledge with no further comment**

Meeting Discussion: None

Question 15
The proposed drug product, NOV03, consists of the drug substance perfluorohexyloctane as the single ingredient in the formulation and contains no additional formulation additives or preservatives. The manufacturing process

consists of [redacted] (b) (4) The three registration batches of the proposed drug product were initially placed on accelerated and long-term stability in the upright orientation only. Subsequently, the three registration batches were placed on accelerated stability in the horizontal orientation. Two of these registration batches were placed on long-term stability in the horizontal orientation.

Since the drug product is pure API (no excipient interaction), the API doesn't absorb water, and there is no expected change in the impurity profile, the Applicant believes that the orientation will have no effect on the stability of the drug product. The Applicant plans to submit the NDA with the following stability data to demonstrate the product remains stable in either horizontal or upright orientation.

Storage condition	Orientation	Amount of Data/Batches
Accelerated (40°C/75%RH)	Upright	6 months/3 batches
	Horizontal	6 months/3 batches
Controlled Room Temp (25°C/60%RH)	Upright	12 months/3 batches
	Horizontal	6 months/2 batches

Based on the rationale presented above, does the Agency agree the Applicant's plan to meet the stability requirement for orientation is acceptable for NDA filing?

FDA Response: Your plan appears reasonable. However, consideration should be given to the container closure system in determining the worst-case scenario for orientation. The registration stability tests should be conducted using batches that represent the commercial manufacturing process and in the to-be-marketed container closure system. Additional one-time studies for E/L (extractable/leachable), photostability, freeze-thaw cycling study with at least 3 cycles, and in-use stability study per ICH stability Q1B guidance are recommended. For further recommendations regarding the batch selection, testing conditions, etc., refer to ICH Q1A (R2) Stability Testing of New Drug Substances and Products.

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

Question 16
The Phase 3 Clinical and registration batches were manufactured at [redacted] (b) (4) utilizing their [redacted] (b) (4) filling machine at a scale of [redacted] (b) (4) kg ([redacted] (b) (4) L), which produced approximately [redacted] (b) (4) units. For commercial purposes, the Applicant plans to manufacture batches at [redacted] (b) (4) utilizing their new [redacted] (b) (4) filling machine, at a scale of [redacted] (b) (4) kg ([redacted] (b) (4) L), producing approximately [redacted] (b) (4) units.

The manufacturing process consists of (b) (4) of the pure drug substance into bottles. (b) (4) The proposed new filling line is capable of meeting capping and torque parameters and the Applicant plans to conduct three consecutive media fills on the proposed (b) (4) line, which would confirm the suitable control of microbial contamination. A comparison of the filling machines is presented in the meeting materials.

Based on the information provided, does the Agency concur with the Applicant's proposal to seek original application approval of the new manufacturing line intended for commercial use by inclusion of data from three consecutive medial fills?

FDA Response: The proposed plan appears reasonable considering the two filling machines are of similar design and operating principle. It is expected that appropriate IQ/OQ/PQ and subsequent process validation activities will be in place to support the new (b) (4) machine and selected process parameters, in-process controls and sampling plans. With regards to your planned NDA submission, please consider addressing the following:

1. Include appropriate extractables and leachables assessments to evaluate risk presented by direct contact manufacturing components when in contact with formulation. A risk assessment could be used to inform what needs to be assessed during extractable and leachable studies. The risk assessment could account for formulation solubilization characteristics; manufacturing process parameters such as processing times and temperatures and product specific factors such as treatment duration and route of administration. Depending on the risks identified, further evaluation via extractable studies of the compounds which migrate from any contact material into the drug product when exposed to exaggerated conditions can be performed in conjunction with leachable studies to understand the chemical components which migrate from contact material into the drug product under normal processing conditions. These studies may then determine appropriate risk mitigation strategies (e.g., flushing fluid lines prior to use). You may choose to refer to the general concepts and principles articulated in USP <1661>, USP<1662> and USP<1663> to support your evaluation of manufacturing systems.

2. Provide comparative details between parameters, in process controls, and sampling plans as well as any procedural/operational differences (e.g., during set-up, flush, restart) between registration and proposed commercial batches.

3. Submit proposed master batch records for commercial batches.
The plan to carry out three consecutive successful medial fills to qualify the new manufacturing line intended for commercial use appears reasonable to support a marketing application. Data from these media fills should be provided in the application at

the time of submission. These media fills should validate the proposed commercial (b) (4) *filling process in the proposed container closure system on the proposed* (b) (4) *line.*
We note that the drug product is multiple-dose, and we note your statement on page 6 of document "1-6-2-meeting-background-materials.pdf" that "the product does not support microbial growth." For a future NDA submission, provide the data demonstrating that the product does not support microbial growth, such as results from USP <51>.
For more information on the type of product quality microbiology information that should be included in a marketing application, please refer to the Agency's 1994 Guidance document: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (https://www.fda.gov/media/71442/download).

Bausch & Lomb Response: Acknowledge with no further comment

Meeting Discussion: None

REGULATORY QUESTIONS
Question 17:
The Applicant intends to submit the application in electronic Common Technical Document (eCTD) format and to cross reference IND 130558.
The Applicant intends to provide in the Module 5 Section of the NDA submission SAS transport files in the SDTM format in addition to the define.xml and blankcrf.pdf documents for each of the Phase 2 and Phase 3 trials. SAS transport files of the analysis datasets (ADaM) and an associated define.xml document will also be included for each study. Analysis datasets for ISS and ISE will be in ADaM format.
The Applicant intends to provide the ISS and ISE descriptive text within the appropriate Module 2 summary sections. The ISS and ISE data sets will be included in Module 5 as illustrated in the eCTD structure presented in the meeting materials document.

An outline of the proposed eCTD structure for the NDA submission is presented in the meeting materials document.

Does the Agency agree that the planned format and content meet the expectations for successful filing of the initial NDA?

FDA Response: We agree, but please note that the Electronic Submissions Gateway (ESG) has been updated to accept chemical structures as structure-data files (SD File)[1]. Please provide all chemical structures (i.e., drug substance, starting materials, intermediates, and impurities) in a single, comprehensive SD File in 3.2.S.3.2 to facilitate efficient review of your NDA. The SD file should include the structure of the drug substance, the structure of each other chemical, the name or abbreviation of each chemical as it appears in the application, NDA Number, and a unique identifier for cross-reference (e.g., Structure 1, Structure 2, etc.). The following data items may also be included if available: UNII code[2], CAS number, role of chemical (e.g., active ingredient, process impurity, degradant,

metabolite, starting material, intermediate)[3]. If you have a substance that requires additional data elements to describe, you can obtain a UNII for the substance by contacting FDASRS@fda.hhs.gov. If you plan to reference a Drug Master File (DMF) for the drug substance in support of your NDA, please work with the DMF holder so that the SD Files would be included in the DMF.

***Bausch & Lomb Response:* Acknowledge with no further comment**

Meeting Discussion: None

Question 18:
Does the Agency agree with the Applicant's intent to request a waiver for the pediatric evaluation?

FDA Response: *Acceptable.*

***Bausch & Lomb Response:* Acknowledge with no further comment**

Meeting Discussion: None

Question 19:
There are no excipients added to the active pharmaceutical ingredient for the drug product formulation of perfluorohexyloctane (b) (4). Therefore, the applicant proposes the USAN to be perfluorohexyloctane (b) (4) with no further evaluation required.

Does the Agency agree with the proposal to submit the USAN as perfluorohexyloctane (b) (4) in the new drug application without further evaluation under the USAN process for assessment?

FDA Response: *The process of selecting a United States Adopted Name (USAN) is made through the USAN Council. You should make a request to USAN Council for an acceptable USAN: http://www.ama-assn.org/go/usan*

***Bausch & Lomb Response:* Acknowledge with no further comment**

Meeting Discussion: None

3.0 OTHER COMMENTS

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

are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

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4744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be 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 that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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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/

WILEY A CHAMBERS
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 130558

MEETING MINUTES

Novaliq GmbH
c/o Strategic Drug Development Services, LLC
Attention: Scott Oglesby, PhD
US Resident Agent
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:

Please refer to your Investigational New Drug Application (IND) for NOV03 Ophthalmic Solution. We also refer to the meeting between representatives of your firm and the FDA on April 10, 2019. The purpose of the meeting was to discuss the clinical Phase 3 development program as well as related CMC and non-clinical topics to support an eventual marketing application for NOV03.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	April 10, 2019 from 3:00-4:00 PM
Meeting Location:	Teleconference
Application Number:	IND 130558
Product Name:	NOV03 Ophthalmic Solution
Indication:	Treatment of Dry Eye Disease (DED)
Sponsor Name:	Novaliq GmbH

FDA ATTENDEES

Wiley Chambers, MD	Deputy Director, DTOP
William Boyd, MD	Clinical Team Leader, DTOP
Rhea Lloyd, MD	Clinical Reviewer, DTOP
Lori Kotch, PhD	Pharmacology/Toxicology Team Leader, DTOP
Andrew McDougal, PhD	Pharmacology/Toxicology Reviewer, DTOP
Aling Dong, PhD	Pharmacology/Toxicology Reviewer, DTOP
Jacquelyn Smith, MA	Senior Regulatory Project Manager
Chunchun Zhang, PhD	Product Quality, OPQ/ONDP/DNDPI/NDPBIII
Ben Zhang, PhD	Product Quality, OPQ/ONDP/DNDAPI/NDBI
Wonyul Lee, PhD	Statistician, OTS/OB/DBIV
Yan Wang, PhD	Statistics Team Leader, OTS/OB/DBIV

SPONSOR ATTENDEES

Christian Roesky, PhD	Managing Director, CEO
Sonja Krösser, PhD	Vice President, Preclinical/ Clinical
Jörg Martin Mauden, PhD	Development Director, CMC
Daniela Willen, PhD	Director, Clinical
Johannes Korward, BSc	Ophthalmology Manager

Consultants

(b) (4)	Clinical Development Consultant
	Regulatory Consultant
	Statistical Consultant

BACKGROUND

On December 7, 2018, Novaliq GmbH requested, via meeting request, an End-of-Phase 2 meeting to discuss the clinical Phase 3 development program as well as related CMC and non-clinical topics to support an eventual marketing application for Novaliq's NOV03. The meeting was granted. On February 14, 2019, the Agency received the meeting package, including questions, from Novaliq. The Agency sent Preliminary Comments to Novaliq on April 3, 2019. The complete list of questions is in **bold** font, the Agency's preliminary responses are in *italic* font and the meeting discussion is in normal font. The discussion begins below.

DISCUSSION

CMC

1. **Does the Agency agree that the drop size evaluation performed during product development is sufficient and including a test for drop size in the stability specification would not be necessary?**

   FDA Response: Yes, we agree.

   No discussion was needed.

2. **Does the Agency agree that the proposed specifications for drug substance and drug product are appropriate for clinical Phase 3 and registration batches?**

   FDA Response: Yes, the proposed approach appears to be reasonable for the drug substance specification.

   The proposed drug product specification is reasonable at this stage of development. We have the following recommendations as your development proceeds towards a NDA:
   - *The proposed specifications indicate that several quality attributes will be tested per European Pharmacopeia. Note that, where applicable, these methods should be demonstrated to be equal or better than the corresponding USP method.*
   - *Include tests for osmolarity with appropriate limits in the drug product specification; refer to USP <771> for further guidance.*
   - *Perform leachables/extractables on the proposed commercial container/closure by using screening analytical methods (such as HPLC, GC etc.) and studies on at least three stability batches through expiry. Refer to USP <1663>, <1664> for recommendations.*

   From a microbiological perspective, the proposed specifications appear appropriate.

   Meeting Discussion
   Novaliq stated that testing for Osmolarity/Osmolality according to USP <785> is not applicable for the final product due to the non-aqueous nature of product. FDA agreed that an Osmolarity specification is not applicable for the product.

3. **Does the Agency agree that the currently available sterile filter validation data are sufficient to support a marketing application?**

   FDA Response: The filter validation studies described appear reasonable to support a marketing application.

   No discussion was needed.

4. **Does the Agency agree on the proposed plan for NDA registration batches?**

   FDA Response: The proposed plan for NDA drug product batches appears reasonable. We recommend that you request a CMC-only meeting at the end of phase 2 to discuss any CMC issues.

   No discussion was needed.

Non-clinical

5. **Does the Agency agree that no additional non-clinical safety studies / data (such as further pharmacology, carcinogenicity and reproduction toxicity studies or chronic or chronic system toxicity are required for inclusion in a future marketing application?**

   FDA Response: We recommend adequate embryofetal (EFD) toxicity studies in one rodent and one non-rodent species, to support the NDA.

   Other than the EFD studies, we concur that no additional nonclinical data are necessary to support clinical trials or the NDA. We do not expect to recommend additional studies to support marketing; a final decision will be made at the time of the NDA review.

   Meeting Discussion

   Novaliq agreed to conduct embryofetal toxicity studies for the compound for inclusion in the NDA. They proposed using rat as rodent and rabbit as non-rodent species as these are the species used in the repeated-dose toxicity studies of the NOV03 program. Novaliq also stated that due to the physicochemical properties of perfluorohexyloctane, not allowing intravenous injection, the EFD toxicity studies are planned to be conducted with oral administration of NOV03. FDA agreed with proposed species and route of administration for EFD studies and recommended the inclusion of toxicokinetic assessments.

Follow-up Question from IND

6. **Does the Agency agree that no further mechanistic investigations on perfluorohexyloctane metabolism or interaction with PPAR are required to support a future marketing application?**

FDA Response: Yes.

No discussion was needed.

Clinical

7. Given the rigorous study design and the consistent, highly significant outcomes on the primary sign (tCFS) and a secondary symptom (Dryness Score [i.e., VAS Severity of Dryness]) endpoints based on a pre-specified analysis plan, does the Agency agree that NVU-002 can be considered one of two pivotal trials for registration?

FDA Response: Study NVU-002 did not include 2-sided p-values and did not adjust for the multiplicity of secondary endpoints. Therefore, the statistical significance of the dryness score endpoint is not clear. Whether Study NVU-002 may be considered one of two pivotal trials, will require review of a complete NDA.

No discussion was needed.

8. Does the Agency agree that the tCFS and Dryness Score are adequate endpoints?

FDA Response: Agree.

No discussion was needed.

9. The proposed corneal staining sign endpoint (tCFS) and Dryness Score symptom endpoint will be taken at Day 57 (week 8) for the QID dosing regimen versus QID saline control.

Does the Agency agree that a trial with a duration of 8 weeks for the primary endpoints is adequate to demonstrate efficacy?

FDA Response: An 8-week trial duration is acceptable; however, we recommend that the control product be a lower concentration than 0.9% sodium chloride.

Meeting Discussion

Novaliq stated that NOV03 does not contain any ingredients other than perfluorohexyloctane; therefore, using the vehicle is not possible. Novaliq stated that they consider a preserved saline solution, 0.9% as the closest to a true placebo which would normally be the vehicle. Novaliq believes that 0.9% saline solution is an adequate comparator because it is isotonic with a determined osmolarity of 290 mOsm/L, and this is within the range of the physiological osmolarity of a healthy tear film. NVU-002 might be considered as one of two pivotal trials, so Novaliq considers it important to provide consistency in terms of the comparator between NVU-002 and NVU-003 trials.

FDA disagreed. Sodium chloride solution, 0.9% is not a particularly comfortable solution to instill in the eyes. While the FDA does not consider sodium chloride solution, 0.9% unsafe, a lower concentration of sodium chloride is strongly preferred as a comparator. FDA noted that the comparator arm for NVU-003 does not have to be the same as that used in NVU-002.

10. Does the Agency agree that further evaluation of the QID regimen is appropriate for the next Phase 3 pivotal trial?

FDA Response: Agree.

No discussion was needed.

11. Does the Agency agree with Novaliq's proposed statistical approach?

FDA Response: No, we do not agree with the use of the Hochberg procedure in multiplicity adjustment for the key secondary endpoints. As stated in the FDA draft guidance "Multiple Endpoints in Clinical Trials Guidance for Industry", the Hochberg procedure is not guaranteed to control the overall Type I error rate for more than two endpoints that have unknown correlation structure. Thus, the use of the Hochberg procedure is not recommended unless you can prove that it adequately controls the overall Type I error rate in the setting of your proposed study. Instead, we recommend either the Bonferroni or the Holm procedure.

Meeting Discussion
Novaliq stated that they have updated the testing of the key secondary endpoints to a mixture of hierarchical testing for the initial 4 endpoints and Hochberg procedure for the remaining 2 endpoints to address the concern regarding Type I error rate. Novaliq shared that the change from baseline in Dryness Score (VAS scale) at Day 15, the change from baseline in total Corneal Fluorescein Staining (tCFS) (NEI scale) at Day 15, the change from baseline of VAS burning/stinging at Day 57 and the change from baseline in central Corneal Fluorescein Staining (NEI scale) at Day 57 are the key secondary endpoints that will be tested hierarchically. If all four of these key secondary endpoints and both primary endpoints demonstrate statistical significance at a 2-sided apha level of 0.05 in favor of NOV03, then two key secondary endpoints, proportion of tCFS responders (≥3 units improvement based on NEI scale) at Day 57 and proportion of Dryness Score responders (≥30 % improvement from baseline) at Day 57 will be tested simultaneously using Hochberg procedure to maintain an overall two-sided alpha level of 0.05. The Agency stated that they agreed with this updated approach.

In addition, the meeting document states that "the primary analysis will use the Full Analysis Set (FAS) with available data per subject". This approach is acceptable only if the proportion of subjects who prematurely discontinue the study prior to Week 8 assessment (due to either lack of efficacy or adverse events) is minimal and balanced between the treatment groups as observed in the completed Phase 2 study. You should encourage the subjects who discontinue study treatment prematurely to stay in the study for all scheduled efficacy and safety assessments.

Meeting Discussion
Novaliq stated that efforts will be made to keep subjects in the trial for all scheduled assessments. Novaliq proposed that if more than 5% of subjects are missing Day 57, missing data will be imputed using MCMC multiple imputation methodology, imputing data from the randomized treatment group as the primary analysis and analysis on available data will be secondary. The Agency agreed with using the FAS with available data if the discontinuation rate is minimal and balanced between the groups. The Agency considered that the MCMC multiple imputation method may not appropriately address potential imbalance between the groups in discontinuations due to adverse event or lack of efficacy in the primary analysis. Novaliq detailed alternative handling of intercurrent events (IcE). The Agency suggested that a baseline observation carried forward (BOCF) rule be considered for the IcE of withdrawal due to lack of efficacy or adverse events for the case of discontinuation >5%.

12. Does the Agency agree that the current clinical PK data are sufficient to further support a future marketing application?

FDA Response: Yes.

No discussion was needed.

13. Is the proposed approach to the initial Pediatric Study Plan presented in the briefing package consistent with the Agency's understanding of the relevant DED populations?

FDA Response: Yes. Your plan to submit an initial pediatric study plan (iPSP) requesting a full waiver for dry eye disease studies in pediatric patients since the disease rarely occurs in children is acceptable.

No discussion was needed.

Regulatory

14. Does the Agency agree with the proposed safety database and the planned safety assessments for a future marketing application?

FDA Response: In addition to the proposed safety database, your postmarketing safety data from the EU market should also be included in a future marketing application.

No discussion was needed.

15. Does the Agency agree that the two proposed pivotal trials, NVU-002 and NVU-003 (if positive on the proposed endpoints) will support labeling for the target indication "treatment of DED associated with MGD?

FDA Response: Labeling is a review issues that requires the review of a complete application. We do acknowledge the proposed meibomian gland dysfunction enrollment

criteria. Please provide an explanation of why safety and efficacy of NOV03 would not be generalizable to the full dry eye disease population.

No discussion was needed.

ADDITIONAL COMMENTS

PREA REQUIREMENTS

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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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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/s/

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