CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208219Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND102654

MEETING MINUTES

Bausch and Lomb Inc.
Attention: Mary Harrell
Senior Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lotemax (loteprednol etabonate ophthalmic gel) 0.38%.

We also refer to the teleconference between representatives of your firm and the FDA on January 30, 2018. The purpose of the meeting was to discuss the Nonclinical, Clinical, and Chemistry, Manufacturing and Controls (CMC) programs and gain agreement on the proposed programs and overall organization of the NDA.

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

If you have any questions, call Ms. June Germain, Safety Regulatory Project Manager at (301) 796-4024.

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: Pre-NDA

Meeting Date and Time: January 30, 2018; 10:00 am-11:00 am EST
Meeting Location: Teleconference

Application Number: IND 102654
Product Name: loteprednol etabonate ophthalmic gel

Indication: treatment of inflammation and pain following ocular surgery
Sponsor/Applicant Name: Bausch and Lomb, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: June Germain, MS

FDA ATTENDEES

Wiley Chambers, MD	Deputy Division Director
William Boyd, MD	Medical Team Leader
Martin Nevitt, MD	Medical Reviewer
Rhea Lloyd, MD	Medical Reviewer
Yan Wang, PhD	Statistical Team Leader
Wonyul Lee, PhD	Statistical Reviewer
Aaron Ruhland, PhD	Pharmacology/toxicology Reviewer
Phillip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
ChunChun Zhang, PhD	Quality Team Lead
June Germain, MS	Safety Regulatory Project Manager

SPONSOR ATTENDEES

Isabelle Lefebvre, MSc. RAC	Vice President, Regulatory Affairs
Kwame Obeng, Ph.D., MSE	Vice President, Regulatory Affairs - CMC
Mary Harrell, BsBM, RAC	Senior Director, Regulatory Affairs
Vishwas Ganu, Ph.D.	Director, Regulatory Affairs - CMC
Eric Phillips, B.S.	Senior Research Scientist, R&D
William Jo, Ph.D.	Director, Nonclinical R&D
Ezra Lowe, Ph.D.	Director, Clinical Pharmacology
Johnson Varughese	Vice President, Clinical Services
Jason Vittitow, Ph.D.	Senior Director, Clinical Affairs R&D
Sandra Narain B.S.	Senior Clinical Trial Manager

1.0 BACKGROUND

On October 17, 2017, Bausch and Lomb requested a pre-NDA meeting to discuss completed Nonclinical, Clinical and Chemistry, Manufacturing and Controls (CMC) studies in preparation for an NDA filing for loteprednol etabonate ophthalmic gel, 0.38% for the treatment of inflammation and pain following ocular surgery. The meeting was granted for January 30, 2018. The briefing package was submitted on December 20, 2017 and preliminary comments in response to the question posted there were sent to Sponsor on January 25, 2018. The Sponsor provided a response to FDA comments on January 29, 2018.

2.0 DISCUSSION

Nonclinical Questions

Question 1

a. Does the Agency agree in principle that the nonclinical package is adequate to support a substantiated review and registration of LE gel 0.38% for the treatment of post- operative inflammation and pain?

FDA comment: We agree.

Bausch & Lomb Response: Acknowledge with no further comment

b. The Agency noted that rabbit LE systemic exposure following topical ocular administration of LE gel 0.38% was higher than Lotemax gel, 0.5%. The Agency recommended in written response letter dated 19 Oct. 2013, that exposure is adequately covered in systemic toxicity studies. Based on the safety factors and systemic safety discussion presented, does the Agency agree in principle that LE human exposure, as characterized in the LE gel 0.38% clinical PK study (881), is adequately covered in the LE systemic toxicity studies summarized in this briefing package?

FDA comment: We agree

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

c. The Sponsor proposes to use similar toxicity labeling as Lotemax gel, which was based on the studies previously submitted to the Lotemax gel NDA. Does the Agency agree that the existing nonclinical data as outlined in this briefing document is sufficient to support LE gel 0.38% labeling, including pregnancy, genotoxicity, carcinogenicity, and impairment of fertility?

FDA comment: We agree. Please note that labeling for Section 8 should be now be formatted to be in accordance with the Pregnancy and Lactation Labeling Rule (PLLR) format. Please refer to the following guidance for more information: https://www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guidances/ UCM425398.pdf

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

Clinical Questions

Question 2

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 Comment: This package supports filing for the new formulation for the proposed indication. Determination of safety and efficacy is a review issue.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

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

FDA comment: Ultimately, the dosing regimen is a review issue; the summary data provided in the meeting package appears to support dosing three times a day for the post-operative indication and it is expected that the submission of full study reports would support the clinical portion of filing the application.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

c. Does the Agency agree the overall safety population, evaluation and presentation adequately supports the new formulation in the claimed dosing regimen (TID)?

FDA comment: We agree

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

Biostatistics Questions

Question 3

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

FDA comment: We agree

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

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

FDA Comment: Yes, we agree, as long as the individual full study reports are also submitted.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

c. Does the Agency agree with the overall plan for presentation of the integrated safety and efficacy summaries within the NDA?

FDA comment: We agree

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

d. Does the Agency agree that it is acceptable to rely on individual study data listings and not provide integrated listings of the data summarized in the ISS and ISE?

FDA comment: We agree

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

Chemistry, Manufacturing and Controls (CMC) Questions

Question 4

a. Based on the specifications provided in Table 1-2 (Appendix-2), does the Agency have any recommendations on the continued use of the current release and shelf-life specifications for (b) (4) LE API?

FDA comment: We currently do not have any recommendations. The acceptability of your release and shelf-life specifications for (b) (4) LE API will be reviewed in your NDA submission.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

b. Based on the specifications provided in Table 2-5 (Appendix-2), does the Agency have any recommendations for commercial release and stability specifications proposed for the drug product LE 0.38% Gel?

FDA comment: We note that the proposed drug product specifications for the LE 0.38% Gel do not include specifications on particulate matter, (b) (4), and have generally higher limits on related substances. Provide justifications in the NDA why these and any other quality attributes were not included. Note that upon review of the data submitted, additional tests and/or tightening of the acceptance limits may be required.

Release and stability specifications proposed for the drug product Loteprednol Etabonate Ophthalmic Gel, 0.38 % Gel are adequate. The product is to meet specification for the USP <71> sterility test method and meet USP requirements for antimicrobial effectiveness testing.

Bausch & Lomb Response: We acknowledge the Agency's comment that our current specifications do not include a test for particulate matter and agree to include a test similar to the Particulate Matter test, approved by the Agency, for LE 0.5% Gel (NDA 202872), at release of LE 0.38% Gel process validation batches and at the time of release of commercial

product. The test approved for LE 0.5% Gel is to examine visually for absence of foreign matter in gel preparation.

Our proposed specifications did not include [redacted] (b) (4) because this is a leachable that originated from [redacted] (b) (4)

The acceptance criteria for related substances "appear" higher because the acceptance criteria for the related substances are established taking into account the approved limits for the Loteprednol Etabonate Ophthalmic Gel, 0.5% formulation. Because the impurities are calculated as a percent of the label claim, the limits were adjusted to account for the difference in label claim for Loteprednol etabonate 0.38% Gel formulation. In NDA, we will provide data supporting the proposed specifications.

We acknowledge Agency's comment and confirm that our methods comply with the current USP chapters <71> for sterility and <51> for anti-microbial effectiveness.

Meeting Discussion:
The Division agreed.

Question 5

a. **Based on the stability protocols and stability batch information, does the Agency agree that stability data from 2 lots of [redacted] (b) (4) kg commercial scale batches and 3 lots of [redacted] (b) (4) kg is sufficient to meet the filing requirement for the New Drug Application?**

FDA comment: Please clarify if these stability batches were manufactured at the intended commercial manufacturing site.

Bausch & Lomb January 29, 2018 response: All the stability batches were manufactured at Bausch & Lomb facility in Tampa, Florida, the intended commercial manufacturing site.

Meeting Discussion:
The Division agreed.

b. **The Sponsor intends to propose shelf-life based on real-time long-term (25°C/40% RH) drug product stability data. Does the Agency consider submission of drug product stability data under intermediate (30°C/65% RH) and/or accelerated conditions (40°C/20% RH) a "requirement" to receive approval of the proposed shelf-life?**

FDA comment: Drug product shelf-life may be granted based on real-time long-term drug product stability data, in which case the drug product stability data under intermediate and accelerated conditions are not required in the NDA. Adequacy of the long-term drug product stability data will be reviewed at the NDA.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

c. Does the Agency agree that the stability programs described in the briefing package for the process validation and routine commercial stability lots are acceptable?

FDA comment: The stability protocol for validation and annual stability batches of DP appear to be reasonable. Acceptability will be determined when the complete data package is submitted for review in the NDA.

The product is to meet specification for USP <71> and meet USP requirements for antimicrobial effectiveness. The drug product will also be tested for sterility and antimicrobial effectiveness at expiry and beyond (up to 36 months).

For more information on the type of data that should be included in proposed NDA, please refer to the following Guidance: Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994).

Bausch & Lomb January 29, 2018 response: We acknowledge Agency's comment and confirm that our methods comply with the current USP chapters <71> for sterility and <51> for anti-microbial effectiveness. Furthermore, these tests will be conducted at expiry and beyond (up to 36 months) and data included will comply with the Agency's guidance cited above.

Meeting Discussion:
The Division agreed.

Regulatory Questions
Question 6
Does the Agency agree that the planned format and content meet the expectations for successful filing of the initial NDA?

FDA comment:
A. Your plan for the drug substance appears reasonable. However, for ease of review, we recommend the following:

1. Submission of eCTD modules: 3.2.S.1 (general information), 3.2.S.2.1 (manufacturers), 3.2.S.3.2 (impurities), 3.2.S.4.1 (specification), 3.2.S.4.4 (batch analysis), 3.2.S.7 (stability).

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

2. Provide a risk assessment for potential mutagenic impurities per ICH M7 and elemental impurities per ICH Q3D.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

3. *Provide an updated drug substance specification.*

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

4. *Provide batch analysis data for recent drug substance batches that is representative of your process.*

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

5. *Confirm your proposed retest date for the drug substance.*

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

6. *List on your 365h form and provide a right of reference for any drug substance DMFs that are needed to support this NDA.*

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

7. *In tabular format, clarify any changes to the manufacturing process for the* (b) (4) *drug substance loteprednol etabonate compared to the process found in NDA 202872. Alternatively, provide a statement in the NDA submission stating the processes are equivalent.*

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

B. *Please submit SAS programs used for the safety and efficacy analyses of each study and the integrated summaries of safety and efficacy.*

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

C. *Submit PK dataset, bioanalytical report and method validation report in addition to clinical/PK study report for Study 881 at the time of NDA submission. Regarding the PK dataset, we ask that you provide the related dataset electronically as a SAS transport file (*.xpt).*

Bausch & Lomb January 29, 2018 response: Acknowledged with no further comment.

D. *Provide data in the NDA to demonstrate that the repeated gel-fluid transition does not adversely impact product quality over the in-use period.*

Bausch & Lomb Response: We will provide the following information in appropriate sections in the NDA:

A study was conducted to assess the effect of repeated gel-fluid-gel transitions experienced by the product when dispensed through the bottle dropper tip throughout the 14 day patient use period. The impact of repeated dosing (shear thinning) events on the product quality was evaluated and tested for assay, dose weight, viscosity and particle size.

The product lots tested do not show significant changes throughout the use period. This indicates that dispensing of the product during the patient use period will be uniform and that repeated dosing will not have a significant impact on the product.

Based on these results, an in-use study over 28-days was conducted on drug product packaged in the proposed market container closure system and viscosity, a critical quality attribute representative of a non-settling gel formulation was assessed along with other quality attributes (e.g. Assay, Related substances etc.). At the end of 28 day use period, all attributes, including viscosity, met the acceptance criteria.

Meeting Discussion:

- The Division had no further comment and noted that it would be an NDA review.

E. *We note that the proposed DP container is an opaque bottle. In the NDA, provide data to show how much shaking of the bottle by the end users is required to result in the gel turning into a liquid ready for dispensing. Consider including specific instructions for the shaking of the bottle in the Package Insert if necessary.*

Bausch & Lomb January 29, 2018 response: In the NDA we will provide the data demonstrating that drops dispensed after inverting the closed bottle (upside down) and shaking it once will deliver product as packaged performs adequately with respect to uniformity of the dose delivered, and that the product remained fairly homogeneous over the course of the dispensing operation.

Meeting Discussion:

- The Division requested that the Sponsor consider the statement that should be included in the labeling for prescribers regarding the amount of time required between shaking and administration of the product.
- The Sponsor agreed.

Question 7

a. Does the Agency confirm that a waiver from conducting the pediatric study requirement (PREA) for the pediatric population 0-18 years of age is applicable and the request would be granted for this NDA?

FDA Comment: Study 670 appears have been designed to provide an assessment of loteprednol gel in the treatment of postoperative inflammation. The Agency's review of the supplemental application for NDA 202872, which includes Study 670 has not been completed and therefore it has not been determined whether the proposed new formulation of loteprednol would require an additional pediatric study.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

Meeting Discussion:

- The Division noted that a change in formulation does not trigger PREA; PREA requires new applications (or supplements to applications) for a new active

ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral.

- The Division noted that the pediatric requirement will be considered in the current NDA 202872/Supplement 002 under review and if that current study is not satisfactory then the need for a pediatric postmarketing requirement will be determined at that time.

b. If not, does the Agency agree

i. that the proposals regarding the pediatric evaluation are acceptable?

ii. that a deferral for the completion of the study prior to NDA filing is acceptable without prejudice to the NDA filing?

FDA Comment: Determination regarding the acceptability of pediatric evaluation proposals will be made after the completion of the supplemental application review for NDA 202872.

Submission of additional pediatric evaluations will be deferred until after completion of the supplemental application review and is not expected to prejudice NDA filing of the 0.38% gel formulation.

Bausch & Lomb January 29, 2018 response: Acknowledge with no further comment.

Meeting Discussion:

- The Division recommended that in the upcoming NDA 208219, the Sponsor reference the pending NDA 202872/Supplement 002, as part of the pediatric section (1.9 for eCTD submissions), to prevent any filing issues.
- The Sponsor stated that NDA 208219 is targeted to be submitted end of March 2018.

3.0 OTHER INFORMATION

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* and *Pregnancy and Lactation Labeling Final Rule* 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of May 5, 2017, the following submission types: NDA, ANDA, and BLA must be submitted in eCTD format. Commercial IND and Master File submissions must be submitted in eCTD format beginning May 5, 2018. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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.				

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

/s/

WILEY A CHAMBERS
02/20/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102654

MEETING MINUTES

Bausch & Lomb, Inc.
Attention: Mary Harrell
Senior Manager, Global Pharmaceutical Regulatory Affairs
7 Giralda Farms, Suite 1001
Madison, NJ 07940

Dear Ms. Harrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for loteprednol etabonate ophthalmic gel, (b)(4)%.

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2013. The purpose of the meeting was to discuss the development plan for a new loteprednol etabonate ophthalmic gel formulation.

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 Ms. June Germain, Acting Safety Regulatory Project Manager at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: guidance

Meeting Date and Time: June 10, 2013, 9:00 AM TO 10:00 AM EDT
Meeting Location: Teleconference

Application Number: IND 102654
Product Name: loteprednol etabonate ophthalmic gel, (b)(4)%

Indication: post operative inflammation and pain following ocular surgery

Sponsor/Applicant Name: Bausch and Lomb, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: June Germain, MS

FDA ATTENDEES

Wiley Chambers, MD	Deputy Director
William Boyd, MD	Medical Team Leader
Martin Nevitt, MD	Medical Reviewer
Jennifer Harris, MD	Medical Reviewer
Rhea Lloyd, MD	Medical Reviewer
Aaron Ruhland, PhD	Pharm/Tox Reviewer
Lori Kotch, PhD	Pharm/Tox Team Leader
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
Phillip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Yan Wang, PhD	Statistical Team Leader
Lin Qi, PhD	Product Quality Reviewer
June Germain, MS	Acting Safety Project Manager

SPONSOR ATTENDEES

Richard D'Souza, PhD	Vice President, Research & Development and Global Regulatory Affairs
Sharon Tonetta, PhD	Vice President, Global Pharmaceutical Regulatory Affairs
Isabelle Lefebvre, MSc.RA,	Director, Global Pharmaceutical Regulatory Affairs
Mary Harrell	Senior Manager, Global Pharmaceutical Regulatory Affairs
Kathleen Krenzer, OD, PhD	Principal Scientist, Nonclinical Safety
Shellise Glogowski, MS	Sr. Research Scientist, Drug Metabolism & Pharmacokinetics
Timothy McNamara, PharmD	Vice President, US Clinical Research
Tomi Luan, OD, PhD	Director, Clinical Affairs

Xiaohui (Ed) Luo, PhD	Director, Biostatistics and Data Management, Pharmaceutical Clinical Affairs
Albert Elion-Mboussa, MS	Sr. Statistician, Clinical Statistics
Kristy Quinzi	Senior Program Manager, Research & Development
Martin Coffey, PhD	Sr. Principal Scientist, Pharmaceutical Product Development

1.0 BACKGROUND

On March 19, 2013 Bausch & Lomb, Inc. requested a Type B meeting to discuss development plans for the new loteprednol etabonate ophthalmic gel formulation.

The face to face meeting was granted for June 10, 2013. The briefing package was submitted on May 9, 2013 and preliminary comments in response to the questions posted there were emailed to the sponsor on June 7, 2013. On June 7, 2013 the sponsor indicated that they were seeking further clarification on questions 2, and 6 and requested the meeting be converted to a teleconference.

2.0 DISCUSSION

QUESTIONS:
NonClinical:
1. Does the Agency agree that, the proposed nonclinical testing strategy and supporting legacy LE data, adequately support the initiation of the proposed clinical studies and the registration of the 0.38% sub-micron formulation?

FDA Response: *The overall approach may be adequate to support initiation of clinical studies, if the following conditions are met. The nonclinical data used to support the new formulation should:*

- *provide adequate systemic and ocular exposure coverage (be equal to or higher)*
- *support the duration of the planned clinical study (≥14 days)*
- *include assessment of standard ocular endpoints (e.g. gross examination, slit lamp biomicroscopy, funduscopy, tonometry, ocular histopathology and ocular irritation).*

The adequacy of the data to support the proposed clinical study and eventual registration will be determined upon review of the full study reports.

Meeting Discussion:
No further clarification

Clinical:
Bausch & Lomb has determined through a rabbit pharmacokinetic study (*See supporting documentation available in Section 1.6.2.10.1)* that the new formulation provides significantly greater levels of loteprednol etabonate in the aqueous humor relative to the current loteprednol etabonate gel formulation. The data gathered to date provides

sufficient information to develop a hypothesis to be further evaluated in the first Phase 3 study (Protocol No. 842) and confirmed in the 2nd Phase 3 study (Protocol No. 843).
1. The design of each study is delineated in the synopses of Study #842 and #843, provided in Attachment 1 and 2 respectively. Does the Agency agree with the rationale provided for the selection of the 0.38% concentration proposed to be assessed in the Phase 3 trials?

FDA Response: *A determination of whether your rationale for the selection of the lower concentration of loteprednol is appropriate will require clinical confirmation.*
The designs of the clinical trials provided in the synopses are acceptable to study the 0.38% concentration and dosing.

Meeting Discussion:
No further clarification

2. Does the Agency agree that the clinical program described in the briefing package would adequately support the Agency's evaluation of safety and efficacy for the proposed indication?

FDA Response: *Potentially, yes. Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting*
The PSP 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. For additional guidance on submission of the PSP, including a PSP Template, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

We note that you are planning to compare the plasma loteprednol concentrations in rabbits following repeated topical ocular administration of the 0.38% gel (submicron-sized particles) and the current 0.5% Lotemax gel (given 1-2 drops per eye QID). If the plasma exposure to the drug achieved from the 0.38% gel is similar to or higher than that from the current 0.5% Lotemax gel in the rabbits, we recommend that you include in your clinical development program a PK study to measure plasma exposures in humans following repeated topical ocular administration of the to-be-marketed 0.38% gel formulation at the proposed clinical dosing regimen.

June 7, 2013, sponsor email response: We have studied PK in rabbits comparing 0.4% and 0.7% concentrations in the gel formulation and have not been able to detect a difference in plasma concentrations (Reference study number 6104-295 provided in Section 1.6.2.10 Table 3 of the briefing package). We have data in humans from a previous study with a 0.5% suspension formulation. Given that we are conducting a PK study in rabbits comparing the 0.38% to the 0.5% gel formulations, if the two formulations do not show a difference in plasma

concentrations, or if the 0.38% formulation shows a lower plasma concentration, can we assume that we will not need to do a human PK study?

Meeting Discussion:

- The sponsor clarified that there will be 3 rabbits per formulation in the planned PK study to measure plasma concentrations of the drug.
- The Division stated that a human PK study will not be required if the point estimate for the systemic exposure to loteprednol (i.e., AUC, Cmax, concentration at other time points) in rabbits for the 0.38% new formulation is numerically lower than that measured with the current 0.5% gel formulation. However, if the systemic exposure to loteprednol is not numerically lower then the data would have to be reviewed to make a determination.

3. Does the Agency have any comments regarding the dose regimen or study design as outlined in the synopses?

FDA Response: *The designs of the clinical trials provided in the synopses are acceptable to study the 0.38% concentration and dosing. We may have additional comments when the actual protocols and statistical analysis plans are submitted.*

Meeting Discussion:
No further clarification

4. Is the total number of subjects exposed to the 0.38% formulation across both studies adequate to evaluate the safety profile for registration?

FDA Response: *Yes. Study 843 is enrolling in a 1:1 ratio (drug/vehicle); you may wish to consider enrolling in a 2:1 ratio.*

Meeting Discussion:
No further clarification

5. Is the masking approach outlined in Study 842 synopsis provided in Attachment 1 acceptable to the Agency?

FDA Response: *Study 842 is enrolling in a 2:2:1:1 ratio (LE 0.38% TID and BID; and Vehicle TID and BID); the masking approach is acceptable.*

Meeting Discussion:
No further clarification

Statistics:

6. Does FDA agree that the sample size of the studies as outlined in the synopses would adequately support the Agency's evaluation of efficacy and safety for the proposed indication?

FDA Response: *Agree from an efficacy evaluation perspective.*

June 7, 2013, sponsor email response: The Agency's response states only "an efficacy evaluation" when the question included "evaluation of efficacy and safety." We would like to understand and seek clarification regarding the evaluation of safety.

Meeting Discussion:

- The Division recommended submitting an application with 500 patients if the to-be marketed concentration provides exposure that is higher than the other loteprednol formulations in the study eye. If exposure to subjects from the 0.38% is found to be at or below the concentrations seen with the other loteprednol formulations, then the safety evaluations for the 0.38% would be looked at in conjunction with the previous loteprednol formulations.

7. Does the Agency agree with the statistical methods that will be used to analyze the data as outlined in the attached synopses to support the proposed indication?
The primary approach to handle missing data is to treat missing data as failure in the ITT population. In addition, we use the last observation carried forward (LOCF) method to impute the missing data for the ITT population and provide analysis on observed data for the PP population in the synopses.

FDA Response: *The statistical methods outlined in the protocol synopses are acceptable.*

Meeting Discussion:
No further clarification

8. Does the agency agree that we have adequate sensitivity analyses to evaluate the impact of missing data?

FDA Response: *Your proposed sensitivity analyses seem adequate provided there is a very small amount of missing data and the missing data are balanced between the treatment groups; otherwise, we recommend you conduct additional sensitivity analysis using multiple imputation approach to further evaluate the impact of missing data. When addressing the issue of missing data, we recommend you consult the book "The prevention and treatment of missing data in clinical trials" authored by the Panel on Handling Missing Data in Clinical Trials (http://www.nap.edu/catalog.php?record_id=12955)"*

Meeting Discussion:
No further clarification

Multiplicity is controlled at two-sided 0.05 level in each study by sequential testing.
a. In Study 842, the hypotheses will be tested sequentially for the two families (for both dosing regimens) and for the two primary efficacy endpoints within each family (within the same dosing regimen family).
b. In Study 843, the hypotheses will be tested sequentially for the two primary efficacy endpoints.

9. Does the agency agree that both studies are qualified as adequate and well controlled studies as Type I error is controlled for the testing of primary efficacy endpoints within each study?
FDA Response: *Agree.*

Meeting Discussion:
No further clarification

Regulatory:
Bausch & Lomb is preparing the proposed drug product package for submission. We anticipate the submission would be acceptable to file as a supplemental New Drug Application (sNDA) to NDA 202872. We also anticipate that upon the complete and satisfactory review of a sufficient scientific package to support the new formulation, NDA 202872 would be granted an additional three (3) years of marketing exclusivity and potential for a new proprietary name.
10. Does the Agency agree with the approach presented above for filing the proposed drug product?

FDA Response: *No. Different strengths or concentrations of one drug substance, if they are the same dosage form intended for the same route of administration, the same general indication(s), and their qualitative composition is the same should be submitted in one application. Since the qualitative composition is changing in your proposal, a new drug application should be submitted.* Decisions regarding marketing exclusivity would be made outside this Division in the Office of Generic Drugs after submission and approval of your application. Decisions regarding the potential for a new proprietary name are made outside this Division by the Division of Medication Error Prevention and Analysis (DMEPA). We recommend you address your concerns regarding a new proprietary name with DMEPA.*

**Please see Guidance for Industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.*

Meeting Discussion:
No further clarification

Based on a proactive approach to mitigate the potential for prescribing and medication errors occurring across the loteprednol etabonate products currently in the market, Bausch & Lomb intends to submit a Request for Review of a New Proprietary Name to IND 102654 for the proposed formulation.

11. Does the Agency have any recommendations or advice regarding supportive information that should be provided in the Request for Review of a New Proprietary Name that would assist the Agency's efforts in determining the potential risk during the safety and promotional evaluation of a proprietary name?

FDA Response: *Decisions regarding the potential for a new proprietary name are made outside this Division by the Division of Medication Error Prevention and Analysis (DMEPA). We recommend you address your concerns regarding a new proprietary name with DMEPA.*

Meeting Discussion:
No further clarification

Based on the extensive safety profile of loteprednol etabonate in multiple formulations and previous pediatric studies conducted with loteprednol etabonate in respective formulations, we plan to extrapolate the data from the 0.38% gel adult studies to support pediatric use.

12. Does the Agency agree with the rationale to request a waiver from conducting the pediatric study requirement (PREA) for the pediatric population 0 – 18 years of age?

FDA Response: No. While efficacy may be extrapolated, safety cannot be extrapolated to a younger population. Please submit your Pediatric plan within 60 Days of the EOP-2 meeting.

Meeting Discussion:

- The sponsor inquired whether a waiver to submit the Pediatric plan within 60 Days of the EOP2 meeting could be granted.
- The Division noted there is no mechanism within the Food and Drug Administration Safety Innovation Act (FDASIS) for granting a waiver to submit the pediatric plan within 60days of the EOP2 meeting. The Division recommended the sponsor look at their pediatric study currently being conducted for the 0.5% formulation which could serve as an adequate dosage form in the pediatric population

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

/s/

WILEY A CHAMBERS
06/27/2013