CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211911Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108324

MEETING MINUTES

Allergan, Inc
Attention: Emily Huang, M.S.
Senior Manager, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612

Dear Ms. Huang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Durysta (bimatoprost (b) (4) implant). We also refer to the telecon between representatives of your firm and the FDA on December 6, 2018. The purpose of the meeting was to obtain FDA agreement on the proposed format and content of the planned Durysta New Drug Application (NDA).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of New Drugs
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: December 6, 2018 from 3:00pm – 4:00pm(EST)
Meeting Location: Teleconference

Application Number: 108324
Product Name: Durysta (bimatoprost (b) (4) implant)

Indication: reduction of intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Sponsor Name: Allergan, Inc

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

Wiley A. Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, M.D.	Clinical Team Leader, DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Rhea Lloyd, M.D.	Clinical Reviewer, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Chunchun Zhang, Ph.D.	Product Quality Team Leader, (OPQ)/Office of New Drug Products (ONDP)
Nancy Waites, Ph.D.	Product Quality Reviewer, OPQ/ Office of Process and Facilities (OPF)
Philip Colangelo, Pharm. D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Aaron Ruhland, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Yunfan Deng, Ph.D.	Statistical Reviewer, OB/DBIV
Roy Blay, Ph.D.	Reviewer, Office of Scientific Investigations (OSI)
Lois Almoza, M.S.	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Yehia Hashad, M.D.	VP and Global Head, Clinical Development
Mike Robinson, M.D.	VP, Clinical Development (Ophthalmology)
Marina Bejanian, Ph.D.	Executive Director, Clinical Development
Margot Goodkin, M.D., Ph.D.	Executive Director, Clinical Development
Jane Zhang, Ph.D.	Director, Biostatistics
Kitty Guo, Ph.D.	Associate Director, Biostatistics
Undraa Altangerel, M.D.	Director, Medical Safety Physician
Mohammed Dibas, Ph.D.	Director Biological Research
Adnan Salameh, Ph.D.	Executive Director, Small Molecule Product Development
Paul Stone, Ph.D.	Vice President, Global Regulatory Affairs
Rory Turk	Director, Global Regulatory Affairs
Karel Cora	Associate Director, CMC Regulatory Affairs
Emily Huang	Senior Manager, Global Regulatory Affairs

BACKGROUND

Bimatoprost ophthalmic solution 0.03% (LUMIGAN® 0.03%) and bimatoprost ophthalmic solution 0.01% (LUMIGAN® 0.01%), both preserved with benzalkonium chloride (BAK), were approved in the United States in March 2001 and August 2010, respectively, for the reduction of elevated IOP in patients with OAG or OHT. Allergan filed an investigational new drug (IND) application for a bimatoprost preservative-free intracameral drug delivery system.

A September 14, 2018, submission from Allergan, Inc. requested a pre-NDA meeting for IND 108324 to obtain FDA agreement on the proposed format and content of the planned Durysta New Drug Application (NDA). The NDA submission is planned for May 2019 and will contain the primary analysis data (3 months) from Studies 192024-091 and 192024-092.

A Meeting Request Granted letter issued on October 3, 2018, stating December 5, 2018, as the agreed upon meeting date. The Meeting Package was received on November 5, 2018. Meeting Preliminary Comments were sent via e-mail, on November 27, 2018. On November 30, 2018, after reviewing the preliminary comments, Allergan sent talking points via e-mail and a request to reclassify their face-to-face meeting to a teleconference.

Due to the Day of Mourning, Federal Offices were closed, Wednesday, December 5, 2018. The Teleconference was rescheduled to Thursday, December 6, 2018 from 3:00pm – 4:00pm (EST).

DISCUSSION

Following, in **bold font**, are the questions in the November 5, 2018, Meeting Package. The FDA responses to these questions are in *italic* font. Talking points from the Sponsor sent via e-mail on, November 11, 2018, at in ***bold, italic*** font. Discussions that took place during the December 6, 2018, teleconference are in regular font.

1. **Regulatory Pathway**

   a. **Does the Agency agree that the original NDA for DURYSTA can be submitted via the 505(b)(1) regulatory pathway under the U.S. Food Drug and Cosmetic Act?**

FDA Response: *Agree.*

Meeting Discussion: None

   b. **Does the Agency agree that data previously submitted to the LUMIGAN 0.03% NDA 21 275 and LUMIGAN 0.01% NDA 22 184 does not require resubmission and can be cross referenced in the original NDA for DURYSTA? If the Agency does not agree, please provide recommendations.**

FDA Response: *Agree.*

Meeting Discussion: None

2. **eCTD Table of Contents**

   Does the Agency agree that the proposed organization of the submission is acceptable? If the Agency does not agree, please provide recommendations.

FDA Response: *Agree.*

Meeting Discussion: None

3. **Financial Disclosure**

   Does the Agency agree with Allergan's proposed list of studies for which clinical investigator financial disclosures will be provided? If the Agency does not agree, please provide recommendations.

FDA Response: *Agree.*

Meeting Discussion: None

4. **ISE and ISS Location**

   Allergan plans to generate a pooled analysis for both efficacy and safety (an integrated summary of efficacy [ISE] and an integrated summary of safety [ISS]). The text portions of the ISE and ISS will be placed in Module 2, Sections 2.7.3 and 2.7.4, respectively. Summary tables, figures, and datasets of the pooled data, along with the respective statistical analysis plans (SAPs), will be provided in Module 5, Section 5.3.5.3. Does the Agency agree with the location of the ISS and ISE within the NDA? If the Agency does not agree, please provide recommendations.

FDA Response: *Agree.*

Meeting Discussion: None

5. **Risk Evaluation and Mitigation Strategy**

   Based on the available data presented in the briefing package, does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) or other risk management activities are not required in the original NDA submission? If the Agency does not agree, please provide recommendations.

FDA Response: *A REMS is not required to be submitted with the original NDA filing for this product. However, a determination of the requirement for a REMS cannot be made until after review of the NDA.*

Meeting Discussion: None

6. **eCRFs and Narratives**

   Does the Agency agree with the plan for the CRFs and narratives to be included in the NDA? If the Agency does not agree, please provide recommendations.

FDA Response: *In addition to the CRFs proposed, it is recommended that CRFs for all discontinued patients (regardless of the reason for discontinuation) be submitted for each study.*

Allergan Response: ***Allergan agrees to include CRFs for all discontinued patients (regardless of the reason for discontinuation).***

Meeting Discussion: None

7. **Study Data Standardization Plan**

   Does the Agency agree with the study data standardization plan (SDSP) for the proposed DURYSTA NDA? If the Agency does not agree, please provide recommendations.

FDA Response: *The plan appears acceptable.*

Meeting Discussion: None

8. **Chemistry, Manufacturing and Controls**

   Does the Agency agree that the planned drug product stability package appears sufficient to support a proposed 36-month shelf life for the drug product? If the Agency does not agree, please provide any recommendations.

FDA Response: *Generally, we expect the NDA at the time of submission to include 12 months long-term and 6-months accelerated stability data for three registration batches. However, the proposed registration stability plan with two batches of 10 µg and three batches of 15 µg drug products is acceptable since the formulation, manufacturing process for* (b) (4) *, sterilization, container closure system, applicator and needle size are the same for both strengths. Please note that the shelf life for the drug product will be determined based on the assessment of the stability information submitted in the NDA.*

Meeting Discussion: None

9. **Does the Agency agree that proposed accelerated drug release specifications for DURYSTA appear acceptable for registration? If the Agency does not agree, please provide recommendations.**

FDA Response: *The acceptability of the drug release specifications for DURYSTA will be a review issue, determined after the submission of the NDA.*

Meeting Discussion: None

10. Does the Agency agree that an implant weight comparison analysis and final release testing data confirmed during commercial process validation is sufficient to demonstrate that implants produced from the new automated implant manufacturing line are equivalent to the Phase 3 implants produced by small scale semi automated process? If the Agency does not agree, please provide recommendations.

FDA Response: The proposed comparability study between the semi-automated and the automated implant manufacturing line appears to be reasonable; however, the FDA does not pre-approve process validation plans and strategies used for process validation studies. The process validation will depend on multiple factors such as actual facility, utilities, qualified equipment, process parameters, control strategies and the trained personnel, some of which are specific to the complexity of the product and manufacturing process. The actual protocols, acceptance criteria, execution, and study outcomes will be evaluated during an inspection. For additional information, please refer to "Guidance for Industry, Process Validation: General Principles and Practices".

There is very limited information on the differences between the phase 3 and the commercial drug products, in terms of the manufacturing processes, the geographical location/ site, scale/ size, and critical parameters for the (b) (4) *process. In vitro drug release testing comparison may be used to support the bridging between the phase 3 and commercial drug products using your proposed accelerated drug release method depending upon the adequacy of the method and the level of changes. It is noted that the drug loaded implant is made* (b) (4) *using polymeric material.* (b) (4) *Critical quality risk could be residual crystalline drug substances into the implant due to improper manufacturing processing condition and raw material variability, polymorphic conversion of the drug over time into the implant since bimatoprost is known to exist in various polymorphs. Such risks may significantly impact the drug release. In absence of a drug release method with sufficient discriminating capability, such risks could not be detected and may remain unmitigated without full understanding on their clinical impact. Therefore we recommend you demonstrate sufficient discriminating capability of the method with respect to above critical CMC attributes of the product and present a side by side full comparison between the Phase 3 and to be commercial sites and manufacturing process focusing on* (b) (4) .

***Allergan Response:* Allergan would like to clarify that the most critical manufacturing unit operation that affects the performance and quality of the drug product is** (b) (4)

The original NDA will contain detailed information on the manufacturing processes, the geographical locations, scale size and critical parameters for [redacted] (b) (4) ***as recommended.***

Meeting Discussion: None

Nonclinical

11. Does the Agency agree the nonclinical data package will provide sufficient information to enable the filing and review of the NDA? If the Agency does not agree, please provide recommendations.

FDA Response: We agree.

Meeting Discussion: None

12. a. Does the Agency agree that [redacted] (b) (4) **?**

FDA Response: No. The proposed explanation is theoretical and should be supported with human imaging data prior to consideration in the labeling of the product.

Meeting Discussion: None

b. Does the Agency agree that the pharmacological data are sufficient to support the review [redacted] (b) (4) **in the Clinical Pharmacology section of the DURYSTA label? If the Agency does not agree, please provide any recommendations.**

FDA Response: No. [redacted] (b) (4) .

Allergan Response: ***Allergan requests confirmation that the availability of human data following treatment with Bimatoprost SR would be sufficient for*** [redacted] (b) (4) .

Meeting Discussion: The labeling of the proposed product is a review issue that will need to be addressed after the new drug application has been submitted and reviewed. The Agency expects the [redacted] (b) (4) to be included [redacted] (b) (4) .

13. Clinical/Statistical - Data for Original NDA and Day 120 Safety Update

a. Does the Agency agree that the proposed clinical data package will provide sufficient information to enable the filing and review of the original NDA?

FDA Response: *Agree.*

Meeting Discussion: None

b. Does the Agency agree that the proposed clinical data package for the NDA 120 Day Safety Update is acceptable? If the Agency does not agree, please provide recommendations.

FDA Response: *Agree. Please note that unmasked adverse events will be assumed to be associated with the drug product.*

Allergan Response: ***Allergan would like to seek clarification on the FDA's comment regarding unmasked adverse events.***

Meeting Discussion: The Agency apologized for the error and revised the meeting response for question 13b to read, "Agree. Please note that **masked** adverse events will be assumed to be associated with the drug product."

14. ISS/ISE analysis plans and subgroups

a. Does the Agency agree with the proposed integration strategy and analyses in the ISS and ISE statistical analysis plans?

FDA Response: *Agree.*

Meeting Discussion: None

b. Does the Agency agree with the proposed ISS and ISE subgroups?

FDA Response: *Disagree. See Guidance for Industry and Food and Drug Administration Staff - Collection of Race and Ethnicity Data in Clinical Trials for recommendations on the presentation of race and ethnicity subgroup categories. Alternatively, if there is a large disparity in enrollment between groups, consideration should be given to presenting subgroup analysis based on iris color since this has been known to potentially impact the safety and/or efficacy of some ophthalmic drugs.*

Allergan Response: ***Phase 3 studies 192024-091 and 192024-092 were initiated prior to the issued date of the Guidance for Industry and Food and Drug Administration Staff - Collection of Race and Ethnicity Data in Clinical Trials (2016), thus the corresponding eCRFs were not designed according to this guidance. Ethnicity was not collected for these 2 studies and no subgroup analysis can be provided based on ethnicity. Race was collected on the eCRF with***

the following categories: Caucasian, Black, Asian, Hispanic, Other, Not Reported, and Unknown.

To incorporate the Agency's comment, Allergan will update the subgroup analysis based on race for each of the racial categories as listed below:

- ***White (Caucasian as collected through the eCRF),***
- ***Asian,***
- ***Black or African American (Black as collected through the eCRF),***
- ***Hispanic***
- ***Other Categories, which includes Other, Not Reported and Unknown***

Does the Agency agree with this approach? If the Agency does not agree, please provide recommendations.

Allergan acknowledges FDA's comment of consideration to a subgroup analysis based on iris color if there is a large disparity in enrollment between groups.

Meeting Discussion: The Agency agreed.

c. Does the Agency have any additional recommendations on the proposed analysis plans for the ISS and ISE? If the Agency does not agree, please provide recommendations.

FDA Response: See 14b.

Meeting Discussion: None

15. Datasets and Data Standards

a. Does the Agency agree with Allergan's plan to provide all datasets, corresponding documentation, and annotated eCRFs for the Phase 1/2 (Study 192024 041D), the 2 pivotal Phase 3 studies (Study 192024 091 and 192024 092), and the ISS/ISE in the proposed NDA?

FDA Response: The plan appears acceptable.

Meeting Discussion: None

b. Based on the submitted draft study data tabulation model (SDTM) dataset definition file and annotated eCRF for the Phase 3 study 192024 091 and draft analysis data model (AdaM) dataset definition files for Phase 3 study 192024 091 and Phase 1/2 study 192024 041D, does the Agency have any suggestions on the data format from a NDA review perspective?

FDA Response: Not at this time.

Meeting Discussion: None

c. Does the Agency agree with Allergan's plan to [redacted] (b) (4) ? If the Agency does not agree, please provide recommendations.

FDA Response: *No. Please submit all the SAS program codes used to produce the efficacy and safety analysis results presented in the study reports of the Phase 3 studies (192024-091 and 192024-092). Please also provide define documents to explain the purpose of the submitted SAS codes.*

Meeting Discussion: Allergan proposed to submit in the original NDA all the SAS program codes used to create ADaM datasets, generate tables and figures associated with primary and secondary efficacy analyses, and generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information in accordance with *Study Data Technical Conformance Guide* v4.2. Allergan will also make all other SAS program codes available upon request. The Agency expected that Allergan's proposal would be acceptable for the NDA filing; and noted that if additional data and programs are found to be needed, the Agency will request them during the NDA review process.

16. Office of Scientific Investigations

Does the Agency agree with the proposed submission plan for summary level clinical site information for the 2 pivotal Phase 3 studies 192024 091 and 192024 092? If the Agency does not agree, please provide recommendations.

FDA Response: *Agree.*

Meeting Discussion: None

17. [redacted] (b) (4)

a. [redacted] (b) (4)

FDA Response: *The contents of the label cannot be determined until a thorough review of the NDA application has been conducted.*

Meeting Discussion: None

b. Does the Agency agree with the approach to include language in the Clinical Studies section of the label to describe [redacted] (b) (4) ? If the Agency does not agree, please provide recommendations.

FDA Response: *The contents of the label cannot be determined until a thorough review of the NDA application has been conducted.*

Meeting Discussion: None

18. Multidisciplinary

a. Based on the data presented in the Briefing Package, are there any additional analyses that should be included in the NDA to assist in the Agency's benefit risk assessment of the product?

FDA Response: *Not at this time.*

Meeting Discussion: None

b. Are there any other points that the Agency feels are important to convey to Allergan regarding the planned DURYSTA NDA?

FDA Response: *We do not consider the product as proposed to be a combination product. As described in 21 CFR 200.50, if the bimatoprost is packaged with its dispenser, the dispenser is considered a drug product, not a combination product.*

Allergan Response: Allergan acknowledges FDA's comment that it does not consider the DURYSTA product a combination (i.e., drug and device). As part of the draft eCTD TOC (see Question 2, Appendix 1) information on the applicator was intended for inclusion in the NDA to satisfy the guidance eCTD Technical Conformance Guide: Technical Specifications Document (November 2017), Section 5 - Combination Products. Considering FDA's position on the product classification, Allergan proposes that information on Design Control (Mod 3.2.R.3 – 3.2.R.7) and the Summative Human Factors Study Report (Mod 5.3.5.4) not be included in the original NDA since there is no device constituent.

Does the Agency agree that the device related documents do not need to be included in the original NDA?

Meeting Discussion: The Agency agreed.

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
12/20/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108324

MEETING MINUTES

Allergan, Inc.
Attention: Emily Huang, M.S.
Senior Associate
2525 Dupont Drive, P.O. Box 19534
Irvine, CA 92623

Dear Ms. Huang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for bimatoprost SR.

We also refer to the teleconference between representatives of your firm and the FDA on January 25, 2014. The purpose of the meeting was to obtain feedback and agreement on the nonclinical registration package and the clinical trial designs and clinical data package required to support registration of the product.

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. Lois Almoza, Regulatory Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

Reference ID: 4572288

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: February 25, 2014 from 9:00AM – 10:00AM(EST)

Application Number: 108324
Product Name: bimatoprost SR
Indication: (b) (4) intraocular pressure inpatients with ocular hypertension or open angle glaucoma
Sponsor/Applicant Name: Allergan, Inc.

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Lim Lucious, M.D.	Clinical Reviewer, DTOP
Philip Colangelo, Pharm. D., Ph.D.	Clinical Pharmacology Team leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Ilona Bebenek, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Yunfan Deng, Ph.D.	Statistical Reviewer, OB/DBIV
Lois Almoza, M.S.	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Scott Whitcup	Executive Vice President
Eric Carter, M.D., Ph.D.	Senior Vice President, Chief Medical Officer
Yehia Hashad, M.D.	Vice President
Michael Robinson, M.D.	Senior Medical Director
Marina Bejanian, Ph.D.	Senior Director
Paul Trennery, Ph.D.	Senior Vice President
Chang Vangyi, B.S.	Principal Scientist
Jacqueline Brassard, DVM, Ph.D.	Research Investigator

Vincent Shu, Ph.D.	Senior Director
Zhiwu Yan	Manager
Chetan P. Pujara, Ph.D.	Senior Director
Gary Charbonneau	Vice President
Rory Turk	Director

BACKGROUND

A December 19, 2013, submission from Allergan, Inc. requested a meeting for IND 108324 to obtain feedback and agreement on the nonclinical registration package and the clinical trial designs and clinical data package required to support registration of the product.

A Meeting Request Granted letter issued on January 3, 2014, stating February 25, 2014, as the agreed upon meeting date. The Meeting Package was received on January 23, 2014. Meeting Preliminary Comments were sent via e-mail, on February 19, 2014.

On February 19, 2014, after reviewing the preliminary comments, Allergan sent via e-mail (Attachment 1), a request to reclassify their face-to-face meeting to a teleconference. On February 20, 2014, Allergan sent via e-mail (Attachment 2), clarification regarding the February 19, 2014 comments and outlined the specific questions they would like to further discuss during the February 25, 2014 meeting.

DISCUSSION

Following, in **bold**, are the questions submitted in the January 23, 2014, Meeting Package. The FDA responses to these questions are in *italics*. Discussions that took place during the February 25, 2014, meeting are in regular font.

Nonclinical:

1. **Allergan believes that the nonclinical data previously submitted for Bimatoprost ophthalmic solution 0.03% (LUMIGAN) and the additional intracameral ocular pharmacology, pharmacokinetics, and toxicity studies in dogs and monkeys are sufficient for approval of Bimatoprost SR for the reduction of IOP in patients with open-angle glaucoma or OHT and additional nonclinical studies are not required.**

   Does the FDA agree that the nonclinical data package is adequate for registration?

   If the FDA does not agree, please provide any recommendations.

   FDA Response:
   Please provide ocular and systemic pharmacokinetic data using the clinical implant.

Meeting Discussion:

Allergan referred to the toxicology summary provided in the meeting briefing package and the pharmacokinetic summary provided in their e-mail dated February 20, 2014, and asked if the Division agreed that the nonclinical data package was adequate for registration.

The Division stated that the adequacy of the nonclinical data submitted to support registration would be a review issue. The Agency commented that based on the data presented in the toxicology and PK summaries (provided in the Feb 20, 2014 email), Allergan may have the nonclinical data they need for registration provided that the data presented in the summaries are representative of the final datasets.

2. **Allergan has conducted ocular toxicity in 2 species (Cynomolgus monkeys and Beagle dogs) to support the development of Bimatoprost SR. In Cynomolgus monkeys, corneal endothelial changes were observed at all implant sizes that were evaluated. Subsequent anterior segment imaging studies revealed that the anterior chamber angle in this species is, in general, too small to adequately fit the implant, resulting in chronic implant contact with the endothelium. A survey of anterior segment biometrics of common toxicology species revealed that only the anterior chamber angle in Beagle dogs during bimatoprost exposure is comparable to the anterior chamber angle of human patients targeted for this therapy.**

   Does the FDA agree that, if any further studies are required to support development and registration, they will be conducted in dogs?

   If the FDA does not agree, please provide any recommendations.

   FDA Response:
   Yes.

   Meeting Discussion: None

Clinical/Statistical:

3. **Allergan is currently conducting a phase 1/2 dose-ranging safety and efficacy trial of Bimatoprost SR (Study 192024-041D Stage 1) for the reduction of IOP in patients with open-angle glaucoma. This repeat-dose trial includes evaluator-masked efficacy (IOP) measurements. The planned enrollment is approximately 100 patients. Allergan proposes to conduct** (b) (4)

Does the FDA agree that this clinical program is adequate to support an NDA for Bimatoprost SR?

If the FDA does not agree, please provide any recommendations.

FDA Response:
No. For a new dosage form, efficacy can be established by either conducting two superiority/non-inferiority trials against an acceptable comparator or one equivalence trial to bimatoprost ophthalmic solution, 0.03%.

Meeting Discussion: None

4. **Based on clinical experience in the dose-ranging trial 192024-041D (6 µg, 10 µg, 15 µg, and 20 µg) and the nonclinical pharmacokinetic/pharmacodynamic data, Allergan intends to include both 10 µg and 15 µg dose strengths in the masked noninferiority trial.**

   Does the FDA agree with the dose strength selection for the masked noninferiority trial?

   If the FDA does not agree, please provide any recommendations.

   FDA Response:
   There does appear to be a trend in efficacy for the 10 µg and 15 µg doses; however, since this is based on a very small sample size and data from the 20µg dose are incomplete, a determination of the dosing strengths to evaluate in phase 3 cannot be determined.

   Meeting Discussion: None

5. **Allergan proposes a 20-month duration for the masked noninferiority trial, in which Bimatoprost SR is administered at baseline, month 4, and month 8. The primary efficacy period will be 12 weeks; all data from scheduled efficacy visits through week 12 will be evaluated for primary efficacy analyses. Additional efficacy data from repeated administrations will be collected through month 12. Safety evaluations will continue through 20 months.**

   Does the FDA agree with the proposed trial duration and primary efficacy time period?

   If the FDA does not agree, please provide any recommendations.

FDA Response:

The duration of the trial and timing of the primary efficacy endpoint are acceptable. There is not enough data available to determine the adequacy of the proposed re-administration interval.

The final protocols need to clearly describe your testing procedure for non-inferiority. We expect the following: the upper limit of the 2-sided 95% confidence interval (CI) of the between-group difference in the mean IOP (tested dose of Bimatoprost SR minus timolol) should be less than 1.5 mmHg at all the pre-specified post baseline time points and less than 1.0 mmHg at the majority.

Meeting Discussion: None

6. (b) (4) **Based on nonclinical and clinical data, a 4-month readministration interval has been chosen for the masked noninferiority trial. Patients in the trial would receive repeat administration (or receive a sham treatment) at months 4 and 8 (with appropriate follow up as described in Question 3).**

Does the FDA agree with the proposed readministration interval for the masked noninferiority trial?

If the FDA does not agree, please provide any recommendations.

FDA Response:

There is not enough data available to determine the adequacy of the proposed re-administration interval. To adequately assess the appropriate dosing interval, multiple doses and re-administration intervals would need to be evaluated in a phase 2 trial.

Meeting Discussion: None

7. **Allergan proposes time-matched IOP as the primary efficacy variable. Mean IOP will be compared between each Bimatoprost SR dose and timolol 0.5% at 8 AM and 10 AM (which correspond to the trough and peak IOP effects of the proposed comparator eye drops when administered in the morning and the evening) at the week** (b) (4) **and 12 visits using the intent-to-treat (ITT) population. While it is known that IOP fluctuates during a 24-hour period, no additional peak and trough IOP effects are expected due to drug release from the sustained-release Bimatoprost SR formulation.**

The primary statistical method on which mean IOP comparisons will be based is a 2-way analysis of variance with treatment/dose groups and baseline IOP stratification as factors. The primary efficacy analysis will test noninferiority of each Bimatoprost SR dose versus timolol, using a noninferiority margin of 1.5 mm Hg. A gatekeeping procedure will be used to control the overall type 1 error rate at 0.05 for each primary analysis timepoint, testing 15 µg against timolol first and following with the comparison between 10 µg and timolol. If the comparison between Bimatoprost SR 15 µg and timolol is not significant at the 0.05 level, the 10 µg versus timolol comparison will not be declared significant regardless of the p-value.

A missing IOP value at a scheduled visit will be imputed with a value calculated the patient's IOP at the same time of day from the last scheduled visit multiplied by a factor. This factor is the ratio of the mean IOP at the corresponding timepoint of the relevant visit divided by the mean IOP at the same time of day of the immediately previous visit based on all patients in the same treatment/dose group who have IOP values at both visits (observed or imputed for the previous visit and observed for the current visit). The imputation will begin from the first posttreatment efficacy visit ((b) (4)), applying the same factor to all patients with missing values at the same timepoint, and will proceed forward for all scheduled visits. Sensitivity analyses of handling of missing data will be performed using alternative methods such as a mixed-effect repeated-measures model or multiple imputation to be detailed in the analysis plan.

a. Does the FDA agree that measuring IOP at 8 am and 10 am is adequate to demonstrate noninferiority to timolol?

FDA Response:
No. The first evaluation after baseline should be between Week 1 or 2, inclusive. The second can be anywhere between Week 6 and 8.

Meeting Discussion: None

b. Does the FDA agree with the proposed primary efficacy analysis up to week 12 for comparisons between each Bimatoprost SR dose and timolol for the proposed indication?

FDA Response:
Agree.

Meeting Discussion: None

c. Does the FDA agree with the proposed statistical model and method of handling missing data for mean comparisons between each Bimatoprost SR dose and timolol?

If the FDA does not agree, please provide any recommendations.

FDA Response:
The proposed statistical model for the primary analysis is acceptable. For the proposed method of handling missing data for mean comparisons between each bimatoprost SR dose and timolol, please provide your rationale for choosing this method and specify its underlying assumption (e.g., missing at random or missing complete at random, or not missing at random).

Meeting Discussion:

The Division recommended to Allergan that they formally submit a detailed, draft proposal for handling missing data; after review of that proposal, the Division would provide comments. Allergan agreed to the Division's recommendation.

8. **For a secondary efficacy analysis, Allergan proposes a noninferiority comparison for mean IOP at each timepoint (8 am and 10 am at weeks (b) (4) and 12) using a (b) (4) mm Hg margin. The analysis will be performed at each visit or timepoint using the same gatekeeping procedure described above (in Question 5).**

   At each timepoint (8 am and 10 am at weeks (b) (4) and 12), a superiority test comparing mean IOP between a Bimatoprost SR dose and timolol will be performed at a 2-sided 0.05 level of significance if noninferiority for the same dose is demonstrated.

   Does the FDA agree with the secondary analysis proposed?

   If the FDA does not agree, please provide any recommendations.

   FDA Response:
   No. The first evaluation after baseline should be between Week 1 and Week 2, inclusive.

   For the analysis of testing non-inferiority, please clarify if a successful outcome requires non-inferiority for every post-baseline time point (6 time points in total) or only for a majority of the post-baseline time points. If it is the second scenario and you intend to make formal statistical inference, you need to address multiplicity issues because there are more than twenty possible successful outcomes. If you intend to treat this non-inferiority criteria (winning at a majority of time points) as only a clinical criteria and without making formal statistical inference, you do not need to address the multiplicity issue.

   For the analysis of testing superiority, please clarify how you plan to claim superiority for testing six pre-specified post baseline time points; please also specify how the Type I error will be controlled for testing superiority of two test treatment doses if both doses of bimatoprost SR demonstrate non-inferiority to timolol. We recommend that your final

protocol provide a complete list (with ranking if applicable) of hypotheses you intend to test and include details on how the overall Type I error rate will be controlled at a level of 5% for 2-sided tests.

Meeting Discussion:
Allergan requested that the Division clarify whether 3 out of 6 timepoints within 1.0 mmHg would satisfy the majority requirement. The Division agreed.

9. **Allergan proposes to use timolol as the comparator for the noninferiority trial.**

   Does the FDA agree?

   If the FDA does not agree, please provide any recommendations.

   FDA Response:
   Agree, timolol maleate ophthalmic solution 0.5% is an acceptable comparator, if two trials are conducted to support the application. Only a single trial may be necessary if the comparator product is bimatoprost 0.03% administered qhs.

   Meeting Discussion: None

10. **Allergan intends to use central corneal endothelial cell density as an inclusion criterion and also to monitor this parameter throughout the clinical trials. A reading center will be employed to evaluate all endothelial cell density data. Allergan proposes to follow the recommendations provided in draft American National Standards Institute (ANSI) standard Z80.27 Implantable glaucoma devices, Table D.1 for minimum endothelial cell density as an inclusion criterion (Draft ANSI Standard Z80.27). Allergan proposes to recheck endothelial cell density for all enrolled patients at 12 and 24 weeks, 12 months, and at the end of the trial, (b) (4) .**

    a. Does the FDA agree with the proposed standard for use as the central corneal endothelial cell density inclusion criterion?

    FDA Response:
    The Agency has no suggested minimum endothelial cell density for inclusion in this trial. The use of the ANSI standard is acceptable, although it is not required for this drug product.

    Meeting Discussion: None

b. Does the FDA agree with the proposed schedule for testing central corneal endothelial cell density during the clinical trials?

If the FDA does not agree, please provide any recommendations.

FDA Response:

Agree.

Meeting Discussion: None

11. **In order to evaluate iris pigmentation change, a previously identified effect of topical prostaglandin treatment, Allergan plans to use measures similar to those used in Study 192024-041D: standard biomicroscopy and iris evaluation. We propose not to include iris photography as a test parameter.**

    Does the FDA agree that iris photography does not need to be included as a test parameter?

    FDA Response:
    Agree.

    Meeting Discussion: None

12. (b) (4)

Meeting Discussion: None

13. **Plasma samples are being collected in ongoing trial 192024-041D for analysis of bimatoprost concentration. Of the 298 samples analyzed from 57 patients (treated with Generation 1 and Generation 2 implants), bimatoprost concentrations were below the lower limit of quantification (1 pg/mL) in 86% of the samples. All observed concentrations were well below the maximum plasma concentration reported after topical administration of bimatoprost 0.03% ophthalmic solution (80 pg/mL). Therefore, Allergan proposes that blood samples for pharmacokinetic analyses not be collected in any of the phase 3 clinical trials.**

    Does the FDA agree that collection of blood samples for pharmacokinetic analyses is not required in any of the phase 3 clinical trials?

    If the FDA does not agree, please provide any recommendations.

    FDA Response:
    Yes, we agree provided that the bimatoprost SR implant used in Phase 3is the to-be-marketed product and with no significant formulation differences compared to that used in Phase 1/2 studies.

    Meeting Discussion: None

14. **Allergan proposes to submit the NDA for Bimatoprost SR after all patients have completed** (b) (4)

    Does the FDA agree with the extent of clinical data that will be included in the original NDA submission and the 120-day safety update?

    If the FDA does not agree, please provide any recommendations.

    FDA Response:
    No. See answer to question #1.

    Meeting Discussion: None

15. Because Bimatoprost SR could represent a safety concern in pediatric patients and would not fulfill an unmet medical need in children, Allergan intends to submit a Pediatric Study Plan requesting a full waiver request for all ages of the pediatric population.

Does the FDA agree that a full waiver from the requirement to conduct studies in the pediatric population is appropriate?

If the FDA does not agree, please provide any recommendations.

FDA Response:
This is a review issue. If bimatoprost SR represents a safety concern in pediatric patients, this information will be included in any future labeling of the product if it is approved.

Meeting Discussion: None

16. While the current applicator (designated as Applicator (b) (4)) has shown adequate safety in nonclinical testing and has been used safely in the ongoing clinical trial, (b) (4)

FDA Response:
Agree.

Meeting Discussion: None

b. Does the FDA agree that if Applicator (b) (4)

If the FDA does not agree, please provide any recommendations.

FDA Response:
No. (b) (4)

Meeting Discussion: None

17 (b) (4)

ATTACHMENTS AND HANDOUTS

Attachment 1	February 19, 2014, e-mail from Allergan, Inc.
Attachment 2	February 20, 2014, e-mail from Allergan, Inc.

Attachment 1

From: Huang_Emily [mailto:Huang_Emily@Allergan.com]
Sent: Wednesday, February 19, 2014 6:19 PM
To: Almoza, Lois
Cc: Willard, Diana M
Subject: RE: Industry Meeting - IND 108324/Allergan, Inc./bimaprost SR

Hi Lois,

Thank you for sending the FDA's preliminary comments for our FDA meeting scheduled on February 25, 2014. The team has reviewed the FDA response and would like to reclassify the face-to-face meeting to a teleconference. We plan to send our response to the FDA's comments prior to the scheduled meeting. If we receive clarification on our response prior to the teleconference and feel that we have the information we need to move forward with the development of our program, we may cancel the meeting.

If you have any questions, please feel free to contact me.

Thank you,
Emily

Attachment 2

From: Huang_Emily [mailto:Huang_Emily@Allergan.com]
Sent: Thursday, February 20, 2014 8:08 PM
To: Almoza, Lois
Cc: Willard, Diana M
Subject: RE: Industry Meeting - IND 108324/Allergan, Inc./bimaprost SR

Hi Lois,

The team has reviewed the Agency's Preliminary Comments and would like to seek clarification on Question 1 and Question 8. Our response to the comments are attached. If we receive clarification on our questions prior to the scheduled teleconference, we may cancel the meeting scheduled for Tuesday, February 25, 2014 at 9am (ET).

If you have any questions, please do not hesitate to contact me.

Thank you,
Emily

Product Name: Bimatoprost SR
Application Number: IND 108,324

Nonclinical:

Question 1 – Nonclinical Registration Package

Allergan believes that the nonclinical data previously submitted for Bimatoprost ophthalmic solution 0.03% (LUMIGAN) and the additional intracameral ocular pharmacology, pharmacokinetics, and toxicity studies in dogs and monkeys are sufficient for approval of Bimatoprost SR for the reduction of IOP in patients with open-angle glaucoma or OHT and additional nonclinical studies are not required.

Does the FDA agree that the nonclinical data package is adequate for registration?

If the FDA does not agree, please provide any recommendations.

FDA Response

Please provide ocular and systemic pharmacokinetic data using the clinical implant.

Allergan Response

The ocular and systemic pharmacokinetic data with clinical implants (Generation 1 and 2) in comparison with topical and other routes of administration are summarized below:

Route of Administration	Species (Allergan Study)	Dose	Systemic Concentration (ng/mL)		Aqueous Humor Concentration (ng/mL)	
			AGN-192024	AGN-191522	AGN-192024	AGN-191522
Intracameral	Dogs TX12102 PK11086	10, 15, and 20 µg 20 µg	BLQ[a] --	BLQ[a]-0.0673 --	-- 13.7	-- 3.4
	Monkey TX09051	30 µg (GEN 1)	0.280	0.165	--	--
	Human 192024-041D	6, 10, 15, and 20 µg	BLQ[b]-0.00398	BLQ[b]-0.0243	--	--
Topical	Dog PK10130	0.03% QD	--	--	BLQ[c]	2.0
	Monkey 6177-100 PK-98-003	0.03% QD 0.1% BID 0.1% BID	0.397 1.92 --	BLQ[d] BLQ[d] --	-- 13.0	-- -- --
	Human PK-98-119 Camras, 2004[e]	0.03% QD 0.03% QD	0.0822 --	2.41 --	-- 2.37	-- 8.55
Intravenous	Monkey 6177-113	0.1 mg/kg/day	124	BLQ	--	--

[a]Lower limit of quantitation (LLOQ) = 0.025 ng/mL (AGN-192024) and 0.05 ng/mL (AGN-191522) in blood ; [b]LLOQ = 0.001 ng/mL (AGN-192024) and 0.010 ng/mL (AGN-191522) in plasma; [c]LLOQ = 0.200 ng/mL (AGN-192024) in aqueous humor ; [d]LLOQ = 0.100 ng/mL (AGN-191622) in blood; [e]Camras et al, Ophthalmology, v111 (2004), 2193-2198.; BLQ = below the limit of quantitation; -- = Data not collected

- In dog, systemic concentrations of AGN-192024 and its metabolite, AGN-191522 after IC administration of the clinical implant are below the lower limit of quantitation (<0.025 ng/mL for AGN-192024 and <0.050 ng/mL for AGN-191522) in a total of 792 samples collected through Day 261 with the exception of 5 samples (representing all dose groups) which had concentrations ranging from 0.0505 to 0.0673 ng/ml, from the ongoing GLP study.

- In the ongoing human clinical study following injection of the clinical implant (6 µg, 10 µg, 15 µg or 20 µg), 298 samples collected up to 24 months post-dose were evaluated for AGN-192024, and 43 samples (14%) had measurable plasma concentrations while the remaining (86%) were below the limit of quantitation (< 0.001 ng/mL). In this study, the highest measured concentration of AGN-192024 was 0.00398 ng/mL (10 µg Gen 1, Week 6). Of the 298 samples evaluated for AGN-191522, three (1%) had measurable plasma concentrations

while the remaining (99%) were below the limit of quantitation (< 0.01 ng/mL) and the highest concentration measured was 0.0243 ng/mL (6 µg Gen 2, Week 20).

- The systemic concentrations of AGN-192024 after clinical implant injection were 20-fold lower (0.00398 ng/mL) than those measured (0.080 ng/mL) following topical dosing of bimatoprost 0.03% ophthalmic solution (LUMIGAN® Package Insert, 2012). The metabolite concentrations were 100-fold (0.0243 ng/mL) lower than those measured (2.41 ng/mL) following topical dosing (Ichhpujani, 2012).

- No adverse drug- or implant-related ocular findings including histology were observed after three repeat injections (9-month interim sacrifice or 5 weeks after the third injection) with 10, 15 or 20 µg Bimatoprost SR implant in the ongoing 18-month GLP dog study.

Based on the toxicology summary provided in the meeting briefing package and the pharmacokinetic summary in this response, does the FDA agree that the nonclinical data package is adequate for registration?

Question 2 – Ocular Toxicity Studies

Allergan has conducted ocular toxicity in 2 species (Cynomolgus monkeys and Beagle dogs) to support the development of Bimatoprost SR. In Cynomolgus monkeys, corneal endothelial changes were observed at all implant sizes that were evaluated. Subsequent anterior segment imaging studies revealed that the anterior chamber angle in this species is, in general, too small to adequately fit the implant, resulting in chronic implant contact with the endothelium. A survey of anterior segment biometrics of common toxicology species revealed that only the anterior chamber angle in Beagle dogs during bimatoprost exposure is comparable to the anterior chamber angle of human patients targeted for this therapy.

Does the FDA agree that, if any further studies are required to support development and registration, they will be conducted in dogs?

If the FDA does not agree, please provide any recommendations.

FDA Response

Yes.

Allergan Response

Allergan acknowledges FDA's comment.

Clinical/Statistical:

Question 3 – Clinical Development Program to Support NDA

Allergan is currently conducting a phase 1/2 dose-ranging safety and efficacy trial of Bimatoprost SR (Study 192024-041D Stage 1) for the reduction of IOP in patients with open-angle glaucoma. This repeat-dose trial includes evaluator-masked efficacy (IOP) measurements. The planned enrollment is approximately 100 patients. Allergan proposes to conduct (b) (4)

(b) (4)

Does the FDA agree that this clinical program is adequate to support an NDA for Bimatoprost SR?

If the FDA does not agree, please provide any recommendations.

FDA Response

No. For a new dosage form, efficacy can be established by either conducting two superiority/non-inferiority trials against an acceptable comparator or one equivalence trial to bimatoprost ophthalmic solution, 0.03%.

Allergan Response

Allergan acknowledges FDA's comment and will conduct 2 non-inferiority studies against a timolol comparator. The number of patients enrolled in the non-inferiority studies will be sufficient to satisfy the safety requirements as described in ICH E1A and obviates the need to

(b) (4)

.

Question 4 – Non- inferiority trial design – Dose selection

Based on clinical experience in the dose-ranging trial 192024-041D (6 µg, 10 µg, 15 µg, and 20 µg) and the nonclinical pharmacokinetic/pharmacodynamic data, Allergan intends to include both 10 µg and 15 µg dose strengths in the masked noninferiority trial.

Does the FDA agree with the dose strength selection for the masked noninferiority trial?

If the FDA does not agree, please provide any recommendations.

FDA Response

There does appear to be a trend in efficacy for the 10 µg and 15 µg doses; however, since this is based on a very small sample size and data from the 20µg dose are incomplete, a determination of the dosing strengths to evaluate in phase 3 cannot be determined.

Allergan Response

Allergan acknowledges FDA's comment.

Question 5 – Non- inferiority trial design – Trial duration and primary efficacy time period

Allergan proposes a 20-month duration for the masked noninferiority trial, in which Bimatoprost SR is administered at baseline, month 4, and month 8. The primary efficacy period will be 12 weeks; all data from scheduled efficacy visits through week 12 will be evaluated for primary

efficacy analyses. Additional efficacy data from repeated administrations will be collected through month 12. Safety evaluations will continue through 20 months.

Does the FDA agree with the proposed trial duration and primary efficacy time period?

If the FDA does not agree, please provide any recommendations.

FDA Response
The duration of the trial and timing of the primary efficacy endpoint are acceptable. There is not enough data available to determine the adequacy of the proposed readministration interval. The final protocols need to clearly describe your testing procedure for non-inferiority. We expect the following: the upper limit of the 2-sided 95% confidence interval (CI) of the between-group difference in the mean IOP (tested dose of Bimatoprost SR minus timolol) should be less than 1.5 mmHg at all the pre-specified post baseline time points and less than 1.0 mmHg at the majority.

Allergan Response
Allergan acknowledges FDA's comment.

Question 6 – Non- inferiority trial design – Re-administration interval

(b) (4)

Based on nonclinical and clinical data, a 4-month readministration interval has been chosen for the masked noninferiority trial. Patients in the trial would receive repeat administration (or receive a sham treatment) at months 4 and 8 (with appropriate follow up as described in Question 3).

Does the FDA agree with the proposed readministration interval for the masked noninferiority trial?

If the FDA does not agree, please provide any recommendations.

FDA Response
There is not enough data available to determine the adequacy of the proposed readministration interval. To adequately assess the appropriate dosing interval, multiple doses and re-administration intervals would need to be evaluated in a phase 2 trial.

Allergan Response
Allergan acknowledges FDA's comment.

Question 7 – Non- inferiority trial design – Primary efficacy analysis
Allergan proposes time-matched IOP as the primary efficacy variable. Mean IOP will be compared between each Bimatoprost SR dose and timolol 0.5% at 8 AM and 10 AM (which

correspond to the trough and peak IOP effects of the proposed comparator eye drops when administered in the morning and the evening) at the week (b) (4), and 12 visits using the intent-to-treat (ITT) population. While it is known that IOP fluctuates during a 24-hour period, no additional peak and trough IOP effects are expected due to drug release from the sustained-release Bimatoprost SR formulation.

The primary statistical method on which mean IOP comparisons will be based is a 2-way analysis of variance with treatment/dose groups and baseline IOP stratification as factors. The primary efficacy analysis will test noninferiority of each Bimatoprost SR dose versus timolol, using a noninferiority margin of 1.5 mm Hg. A gatekeeping procedure will be used to control the overall type 1 error rate at 0.05 for each primary analysis timepoint, testing 15 µg against timolol first and following with the comparison between 10 µg and timolol. If the comparison between Bimatoprost SR 15 µg and timolol is not significant at the 0.05 level, the 10 µg versus timolol comparison will not be declared significant regardless of the pvalue.

A missing IOP value at a scheduled visit will be imputed with a value calculated the patient's IOP at the same time of day from the last scheduled visit multiplied by a factor. This factor is the ratio of the mean IOP at the corresponding timepoint of the relevant visit divided by the mean IOP at the same time of day of the immediately previous visit based on all patients in the same treatment/dose group who have IOP values at both visits (observed or imputed for the previous visit and observed for the current visit). The imputation will begin from the first posttreatment efficacy visit ((b) (4)), applying the same factor to all patients with missing values at the same timepoint, and will proceed forward for all scheduled visits. Sensitivity analyses of handling of missing data will be performed using alternative methods such as a mixed-effect repeated-measures model or multiple imputation to be detailed in the analysis plan.

a. Does the FDA agree that measuring IOP at 8 am and 10 am is adequate to demonstrate noninferiority to timolol?

b. Does the FDA agree with the proposed primary efficacy analysis up to week 12 for comparisons between each Bimatoprost SR dose and timolol for the proposed indication?

c. Does the FDA agree with the proposed statistical model and method of handling missing data for mean comparisons between each Bimatoprost SR dose and timolol? If the FDA does not agree, please provide any recommendations.

FDA Response 7a

No. The first evaluation after baseline should be between Week 1 or 2, inclusive. The second can be anywhere between Week 6 and 8.

Allergan Response

Allergan will incorporate IOP evaluations at 8 am and 10 am between Week 1 or 2, inclusive. The subsequent IOP evaluations will be between Week 6 and 8, and the last evaluations (for the primary analysis) will be at Week 12.

FDA Response 7b

Agree.

Allergan Response
Allergan acknowledges FDA's comment.

FDA Response 7c
The proposed statistical model for the primary analysis is acceptable. For the proposed method of handling missing data for mean comparisons between each bimatoprost SR dose and timolol, please provide your rationale for choosing this method and specify its underlying assumption (e.g., missing at random or missing complete at random, or not missing at random).

Allergan Response
The proposed method of handling missing data is meant to reduce bias which favors the implant in the presence of treatment effect if the traditional LOCF method were used; it makes no underlying assumption of the missing data mechanism. Sensitivity analyses of handling missing data will be specified in the protocol and statistical analysis plan.

Question 8 – Non-inferiority trial design – Secondary efficacy analyses
For a secondary efficacy analysis, Allergan proposes a noninferiority comparison for mean IOP at each timepoint (8 am and 10 am at weeks (b) (4), and 12) using a (b) (4) mm Hg margin. The analysis will be performed at each visit or timepoint using the same gatekeeping procedure described above (in Question 5).

At each timepoint (8 am and 10 am at weeks (b) (4), and 12), a superiority test comparing mean IOP between a Bimatoprost SR dose and timolol will be performed at a 2-sided 0.05 level of significance if noninferiority for the same dose is demonstrated.

Does the FDA agree with the secondary analysis proposed?

If the FDA does not agree, please provide any recommendations.

FDA Response
No. The first evaluation after baseline should be between Week 1 and Week 2, inclusive. For the analysis of testing non-inferiority, please clarify if a successful outcome requires non-inferiority for every post-baseline time point (6 time points in total) or only for a majority of the post-baseline time points. If it is the second scenario and you intend to make formal statistical inference, you need to address multiplicity issues because there are more than twenty possible successful outcomes. If you intend to treat this noninferiority criteria (winning at a majority of time points) as only a clinical criteria and without making formal statistical inference, you do not need to address the multiplicity issue.

For the analysis of testing superiority, please clarify how you plan to claim superiority for testing six pre-specified post baseline time points; please also specify how the Type I

error will be controlled for testing superiority of two test treatment doses if both doses of bimatoprost SR demonstrate non-inferiority to timolol. We recommend that your final protocol provide a complete list (with ranking if applicable) of hypotheses you intend to test and include details on how the overall Type I error rate will be controlled at a level of 5% for 2-sided tests.

Allergan Response
Based on the response to Question 5 (Clinical Question 3), the primary analysis has been adjusted so that all timepoints will be within 1.5 mmHg with a majority within 1.0 mmHg. However, Allergan requests that the FDA clarify whether 3 out of 6 timepoints within 1.0 mmHg will satisfy the majority requirement.

With the change to the primary analysis, the main secondary analysis now will be superiority tests of Bimatoprost SR to timolol. The methodology to control the Type I error of multiple superiority tests will be detailed in the statistical analysis plan.

Question 9 – Non-inferiority trial design – Comparator product
Allergan proposes to use timolol as the comparator for the noninferiority trial.

Does the FDA agree?

If the FDA does not agree, please provide any recommendations.

FDA Response
Agree, timolol maleate ophthalmic solution 0.5% is an acceptable comparator, if two trials are conducted to support the application. Only a single trial may be necessary if the comparator product is bimatoprost 0.03% administered qhs.

Allergan Response
Allergan acknowledges FDA's comment.

Question 10 – Study parameters – Central corneal endothelial cell density
Allergan intends to use central corneal endothelial cell density as an inclusion criterion and also to monitor this parameter throughout the clinical trials. A reading center will be employed to evaluate all endothelial cell density data. Allergan proposes to follow the recommendations provided in draft American National Standards Institute (ANSI) standard Z80.27 Implantable glaucoma devices, Table D.1 for minimum endothelial cell density as an inclusion criterion (Draft ANSI Standard Z80.27). Allergan proposes to recheck endothelial cell density for all enrolled patients at 12 and 24 weeks, 12 months, and at the end of the trial, (b) (4) .

a. Does the FDA agree with the proposed standard for use as the central corneal endothelial cell density inclusion criterion?

b. Does the FDA agree with the proposed schedule for testing central corneal endothelial cell density during the clinical trials?
If the FDA does not agree, please provide any recommendations.

FDA Response 10a
The Agency has no suggested minimum endothelial cell density for inclusion in this trial. The use of the ANSI standard is acceptable, although it is not required for this drug product.

Allergan Response 10a
Allergan acknowledges FDA's comment.

FDA Response 10b
Agree.

Allergan Response 10b
Allergan acknowledges FDA's comment.

Question 11 – Study parameters – Iris photography
In order to evaluate iris pigmentation change, a previously identified effect of topical prostaglandin treatment, Allergan plans to use measures similar to those used in Study 192024-041D: standard biomicroscopy and iris evaluation. We propose not to include iris photography as a test parameter.

Does the FDA agree that iris photography does not need to be included as a test parameter?

FDA Response
Agree.

Allergan Response
Allergan acknowledges FDA's comment.

Question 12 – (b) (4)

(b) (4)

(b) (4)

Allergan Response
As addressed in Question 3 (Clinical Question 1) Allergan will be conducting 2 adequate and well-controlled, phase 3, non-inferiority studies. The number of patients enrolled in the phase 3 studies will be sufficient to satisfy the safety requirements as described in ICH E1A (b) (4)

Question 13 – Human pharmacokinetic data
Plasma samples are being collected in ongoing trial 192024-041D for analysis of bimatoprost concentration. Of the 298 samples analyzed from 57 patients (treated with Generation 1 and Generation 2 implants), bimatoprost concentrations were below the lower limit of quantification (1 pg/mL) in 86% of the samples. All observed concentrations were well below the maximum plasma concentration reported after topical administration of bimatoprost 0.03% ophthalmic solution (80 pg/mL). Therefore, Allergan proposes that blood samples for pharmacokinetic analyses not be collected in any of the phase 3 clinical trials.

Does the FDA agree that collection of blood samples for pharmacokinetic analyses is not required in any of the phase 3 clinical trials?

If the FDA does not agree, please provide any recommendations.

FDA Response
Yes, we agree provided that the bimatoprost SR implant used in Phase 3 is the to-be marketed product and with no significant formulation differences compared to that used in Phase 1/2 studies.

Allergan Response
Allergan acknowledges FDA's comment.

Question 14 – Submission package for the NDA
Allergan proposes to submit the NDA for Bimatoprost SR after all patients have completed (b) (4)

(b) (4)

Does the FDA agree with the extent of clinical data that will be included in the original NDA submission and the 120-day safety update?

If the FDA does not agree, please provide any recommendations.

FDA Response
No. See answer to question #1.

Allergan Response
Allergan acknowledges FDA's comment. As addressed in Question 3 (Clinical Question 1), Allergan will be conducting 2 adequate and well-controlled non-inferiority studies. (b) (4) . At the time of NDA submission, Allergan will provide a minimum of 3 months data on all patients, and 12 months data on at least 100 patients in the 2 adequate and well-controlled studies .

Question 15 – Waiver for studies in pediatric populations
Because Bimatoprost SR could represent a safety concern in pediatric patients and would not fulfill an unmet medical need in children, Allergan intends to submit a Pediatric Study Plan requesting a full waiver request for all ages of the pediatric population.

Does the FDA agree that a full waiver from the requirement to conduct studies in the pediatric population is appropriate?

If the FDA does not agree, please provide any recommendations.

FDA Response
This is a review issue. If bimatoprost SR represents a safety concern in pediatric patients, this information will be included in any future labeling of the product if it is approved.

Allergan Response
Allergan acknowledges FDA's comment.

Question 16 – Change to applicator
While the current applicator (designated as Applicator (b) (4)) has shown adequate safety in nonclinical testing and has been used safely in the ongoing clinical trial, (b) (4)

(b) (4)

(b) (4)

b. Does the FDA agree that if Applicator (b) (4)

If the FDA does not agree, please provide any recommendations.

FDA Response 16a
Agree.

Allergan Response 16a
Allergan acknowledges FDA's comment.

FDA Response 16b
No. (b) (4)

Allergan Response 16b
Allergan acknowledges FDA's comment.

Ouestion 17 – (b) (4)

(b) (4)

(b) (4)

Allergan Response
Allergan acknowledges FDA's comment.

List of References

Ichhpujani P, Katz LJ, Hollo G, Shields CL, Shields JA, Marr B, et al. Comparison of human ocular distribution of bimatoprost and latanoprost. J Ocular Pharmacology and Therapeutics. 2012;28(2):134-145. doi:10.1089/jop.2011.0097.

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