# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214028Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 122483

**MEETING MINUTES**

Allergan, Inc.
Attention: Ms. Claire L. Whitley
Director, Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92623-9534

Dear Ms. Whitley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AGN-190584 (pilocarpine HCl ophthalmic solution).

We also refer to the telecon between representatives of your firm and the FDA on December 11, 2019. The purpose of the meeting was to obtain feedback and agreement from the Agency on the format and content of the pilocarpine HCl ophthalmic solution NDA for treatment of presbyopia.

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 Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:

- Meeting Minutes

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B
**Meeting Category:** Pre-NDA

The teleconference was scheduled as follows:

**Date:** December 11, 2019
**Time:** 11:00 AM – 12:00 PM
**Phone Arrangements:** Call in information provided by Allergan:
Toll number: +1 (213) 282-9940
Conference ID/Passcode: (b) (4)

**Application Number:** 122483
**Product Name:** AGN-190584 (Pilocarpine HCl Ophthalmic Solution)

**Indication:** treatment of presbyopia
**Sponsor Name:** Allergan, Inc.

**Meeting Chair:** William Boyd, M.D.
**Meeting Recorder:** Diana Willard

## FDA ATTENDEES

| | |
|---|---|
| William Boyd, M.D. | Clinical Team Leader, Division of Transplant and Ophthalmology Products (DTOP) |
| Rhea Lloyd, M.D. | Clinical Reviewer, DTOP |
| David Summer, M.D. | Clinical Reviewer, DTOP |
| Chunchun Zhang, Ph.D. | Quality Assessment Lead (Acting), Office of New Drug Products (ONDP)/Office of Pharmaceutical Quality (OPQ)/Drug Product Division III, Branch VI |
| Milton Sloan, Ph.D. | Product Quality Reviewer, ONDP/OPQ/Drug Product Division III, Branch VI |
| Bethanie Lee, Ph.D. | Microbiology Reviewer, OPQ/Office of Pharmaceutical Manufacturing Assessment/ Division of Microbiology Assessment |
| Erin Ruhland, Ph.D. | Pharmacology/Toxicology Reviewer, DTOP |
| Roy Blay, Ph.D. | Regulatory Officer, Office of Compliance/Office of Scientific Investigations/Division of Clinical Compliance Evaluation/Good Clinical Practice Assessment Branch |
| Diana Willard | Chief, Project Management Staff, DTOP |

**ALLERGAN, INC. ATTENDEES**

| | |
|---|---|
| Paul Stone, Ph.D. | Vice President, Regulatory Affairs |
| Claire Whitley, B.Sc. Hons (Int) | Director, Regulatory Affairs |
| Tiffanie Yu, M.S., RAC | Manager, Regulatory Affairs Research |
| Anu Gore, Ph.D. | Executive Director, Small Molecule Product Development |
| Jaya Giyanani, M.S. | Senior Scientist, Small Molecule Product Development |
| Manish Dhawan, M.S. | Senior Manager, CMC Regulatory Affairs |
| Karel Cora, B.S. | Director, CMC Regulatory Affairs |
| Ramakrishnan Srikumar, Ph.D. | Executive Director, Small Molecule Product Development |

**BACKGROUND**

An October 1, 2019, submission from Allergan, Inc. (Allergan) requested a Pre-NDA meeting to obtain feedback from the Agency on the format and content of the pilocarpine HCl ophthalmic solution NDA for the treatment of presbyopia. The October 3, 2019, Meeting Request Granted letter listed December 11, 2019, as the agreed upon meeting date. Meeting Preliminary Comments were sent to Allergan on December 4, 2019. A December 9, 2019, e-mail from Allergan contained a response to the December 4, 2019, Meeting Preliminary Comments and stated that Allergan wished to focus the meeting on Question 7 (stability).

**DISCUSSION**

Following, in **bold**, are the questions submitted in the November 2, 2019, Meeting Package. The FDA responses to these questions are in *italics*. Allergan's comments in the December 9, 2019, e-mail are in ***bold italics*** and the meeting discussion is in regular font.

**Regulatory**

**1. Regulatory Pathway**

**As discussed at the EOP2 meeting, Allergan plans to submit the original NDA for pilocarpine HCl 1.25% ophthalmic solution via the 505(b)(2) regulatory pathway under the US Food Drug and Cosmetic Act. Does the Agency have any additional comments at this time?**

*FDA Response: We have no additional comments.*

Meeting Discussion: None.

**2. eCTD Table of Contents**

**Does the Agency agree that the proposed organization of the submission provided in Appendix 1 is acceptable?**
**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *You have provided a draft table of contents of the eCTD in Appendix 1 of the Briefing Document. We recommend that you create a folder named "**datasets**" in Module 5. Regarding the specific structures of the "datasets" folder, please consult Section 7 (Figure 1 and Table 2) of the Agency's 'Study Data Technical Conformance Guide' document (https://www.fda.gov/media/119807/download). We further recommend that you provide a 'reviewers-guide.pdf' document and a 'define.pdf' document for both the analysis and tabulation datasets of the studies. The programming codes (preferably SAS codes) used to create the analysis datasets and the efficacy and safety tables should also be provided.*

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 any recommendations.**

*FDA Response:* *Agree.*

Meeting Discussion: None.

**4. ISE and ISS Location**

**Allergan plans to generate a pooled analysis for both efficacy and safety (ISE and 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, listings, figures, and data sets of the pooled data, along with the respective SAPs, will be provided in Module 5, Section 5.3.5.3. Does the Agency agree?**
**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *Agree.*

Meeting Discussion: None.

**5. Risk Evaluation and Mitigation Strategy**

**Based on the available information presented in the briefing package, does the Agency agree that a 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:* *Agree.*

Meeting Discussion: None.

**6. Study Data Standardization Plan**

**Does the Agency agree with the SDSP for the proposed pilocarpine HCl 1.25% ophthalmic solution NDA?**
**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *Agree for clinical data standards.*

*For the nonclinical study reports, please see the following recommendations:*

- *Please provide pdf versions of all nonclinical study reports to the NDA. Those nonclinical studies which only investigated oxymetazoline are not required.*
- *For studies initiated after December 17, 2016, we recommend that SEND data be provided for supported domains. We do not recommend creating SEND data sets for the nonclinical ophthalmic endpoints prior to the completion of corresponding data standards.*

*For further general information, please see CDER's webpage for study data standards (https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber).*

*You may email questions (e.g., regarding test datasets or any other issues directly to the CDER eDATA team at cder-edata@fda.hhs.gov. If you contact them, please provide their responses in the NDA application.*

Meeting Discussion: None.

## PRODUCT QUALITY

### 7. Stability Program

**Does the Agency agree that the planned drug product stability data package appears sufficient to support a proposed 24-month shelf life for the drug product in the 1-month supply pack (SP3) and the 3-month supply pack (SP4)? If the Agency does not agree, please provide any recommendations.**

*FDA Response: The shelf life will be determined based on assessment of the stability information (quality attribute evaluation) in the commercial container closure system SP3 and SP4 submitted in the NDA. Naturally, changes to the secondary package may not adversely impact the drug product stability. However, additional results should be provided on the evaluation of the package design improvements for enhanced protective properties and may provide a rationale to support the proposed shelf life.*

**Allergan December 9, 2019, E-mail Response:**

The primary container closure system for the drug product is the same for all four secondary packaging systems. As shown in Figure 1, to enhance patient experience, Allergan developed a secondary packaging system referred to as secondary packaging system 1 (SP1) for Pilocarpine HCl 1.25% drug product. Additional refinement of SP1 was done to create SP2, SP3, and SP4 secondary packaging systems with a goal to reduce waste and further enhance patient convenience (Figure 1). The SP3 and SP4 packaging configurations have been selected for commercialization. Allergan believes that these changes to the secondary packaging systems are not expected to adversely impact drug product stability.

A comparison of the secondary packaging systems is also included in Table 1.

**Figure 1 Secondary Packaging Configurations for Pilocarpine HCl 1.25% drug product**

**Table 1 Comparison of SP1, SP2, SP3 and SP4 Packaging Configurations for Pilocarpine HCl 1.25% Drug Product**

| **Primary Container Closure** | | | | |
|---|---|---|---|---|
| Bottle | 5 mL LDPE bottle, (b) (4) | | | |
| Tip | 15 mm LDPE, 35 µL Control Drop Tip, (b) (4) | | | |
| Cap | 15 mm HIPS, (b) (4) | | | |
| Seal | (b) (4) | | | |
| Label | Paper Label | | | |
| **Secondary Packaging System** | | | | |
| | **SP1** | **SP2** | **SP3** | **SP4** |
| (b) (4) | | | | |

As shown in Table 1, SP3 and SP4 have minimal differences when compared to SP1 secondary packaging system. These enhancements were made only to reduce waste by using less material, (b) (4) and to enhance patient convenience (b) (4).

A risk assessment was conducted to evaluate the impact of these secondary packaging configuration changes. Allergan considers that these changes are not expected to adversely impact drug product stability.

The Risk Assessment was conducted based on the following:

- No changes were made to the Primary Container Closure of SP1, so the product contact surfaces are the same for all configurations.
- Refinements to SP1 Secondary Packaging System only resulted in minor changes to materials and use less packaging material overall.
  - Low likelihood of changes to leachable profile among secondary packaging systems

- o No impact to other chemistry or microbiology parameters.

Based on the risk assessment, Allergan decided to generate additional leachables data in support of the proposed commercial packaging configuration (SP3 and SP4). Therefore, SP3 and SP4 were added to the ongoing stability program for leachables (Table 2 & Table 3). The threshold for leachables have been pre-determined based on safety and analytical capability. If any leachables are observed above this threshold, they will be further characterized, and the appropriate toxicology assessments will be performed.

To support the proposed 24-month shelf-life for pilocarpine HCl 1.25% drug product in SP3 and SP4 configurations, Allergan will submit stability data summarized in Table 2 and Table 3 with a commitment to continue the long-term stability studies through the proposed shelf-life. Allergan intends to provide 12 months of drug product stability data on SP1 at 25°C/40% RH and 6 months at 40 °C/NMT (b)(4)% RH. In addition, Allergan will provide 6 months of leachables data on SP3 and SP4 at 25°C/40% RH and at 40 °C/NMT (b)(4)% RH at the time of NDA filing.

**Table 2 Summary of Stability Data at 25°C/40% RH to be Included in the NDA Filing**

| | | Quality Attribute | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Time Point (mo) | Physical Appearance | Pilo HCl Assay/Imp. | BAK Assay | Osmolality | pH | PMT | Sterility | Leachable (GC method) | Leachable (LC method) |
| SP1 configuration | 0 | X | X | X | X | X | X | X | X | X |
| | 3 | X | X | X | X | X | | | X | X |
| | 6 | X | X | X | X | X | X | | | |
| | 9 | X | X | X | X | X | | | | |
| | 12 | X | X | X | X | X | X | X | | |
| SP2 configuration | 0 | Since there is no change in primary container closure system, data from SP1 configuration is applicable to support shelf-life as determined by risk assessment for impact of secondary packaging configurations. | | | | | | | X | X |
| | 3 | | | | | | | | X | X |
| | 6 | | | | | | | | X | X |
| | 9 | | | | | | | | X | X |
| | 12 | | | | | | | | X | X |
| SP3 configuration | 0 | Since there is no change in primary container closure system, data from SP1 configuration is applicable to support shelf-life as determined by risk assessment for impact of secondary packaging configurations. | | | | | | | X | X |
| | 3 | | | | | | | | X | X |
| | 6 | | | | | | | | X | X |
| SP4 configuration | 0 | Since there is no change in primary container closure system, data from SP1 configuration is applicable to support shelf-life as determined by risk assessment for impact of secondary packaging configurations. | | | | | | | X | X |
| | 3 | | | | | | | | X | X |
| | 6 | | | | | | | | X | X |

Note: Long-term stability studies will continue through the proposed shelf-life.

**Table 3 Summary of Stability Data at 40 °C/NMT (b) (4) % RH to be Included in the NDA Filing**

| | | Quality Attribute | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Time Point (mo) | Physical Appearance | Pilo HCl Assay/Imp. | BAK Assay | Osmolality | pH | PMT | Sterility | Leachable (GC method) | Leachable (LC method) |
| SP1 configuration | 0 | X | X | X | X | X | X | X | X | X |
| | 1 | X | X | X | X | X | | | X | X |
| | 3 | X | X | X | X | X | | | X | X |
| | 6 | X | X | X | X | X | X | | | |
| SP2 configuration | 0 | Since there is no change in primary container closure system, data from SP1 configuration is applicable to support shelf-life as determined by risk assessment for impact of secondary packaging configurations. | | | | | | | X | X |
| | 1 | | | | | | | | X | X |
| | 3 | | | | | | | | X | X |
| | 6 | | | | | | | | X | X |
| SP3 configuration | 0 | Since there is no change in primary container closure system, data from SP1 configuration is applicable to support shelf-life as determined by risk assessment for impact of secondary packaging configurations. | | | | | | | X | X |
| | 1 | | | | | | | | X | X |
| | 3 | | | | | | | | X | X |
| | 6 | | | | | | | | X | X |
| SP4 configuration | 0 | Since there is no change in primary container closure system, data from SP1 configuration is applicable to support shelf-life as determined by risk assessment for impact of secondary packaging configurations. | | | | | | | X | X |
| | 1 | | | | | | | | X | X |
| | 3 | | | | | | | | X | X |
| | 6 | | | | | | | | X | X |

Allergan considers that the totality of stability data from SP1, SP2, SP3 and SP4 to be provided in the NDA will be sufficient to support the proposed 24-month shelf-life for pilocarpine HCl 1.25% drug product.

Meeting Discussion: Allergan reviewed the comments in their December 9, 2019, e-mail response for this question. The Agency stated that the proposed stability data package is reasonable, but that acceptability will be a review issue. The shelf life will be determined as part of the NDA review.

Allergan plans to provide stability update for SP3 and SP4 during the NDA review. Depending on the timing of the update data, the Agency may be able to review the update.

Post-meeting Note: Applications are expected to be complete at the time of the submission. The Agency cannot commit to reviewing additional information submitted during the review of the application.

**CLINICAL/STATISTICAL**

**8. Data for Original NDA and 120-Day Safety Update Based on Literature Review**

**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 data package for the NDA 120-Day Safety Update based on literature review is acceptable?**

*FDA Response:* *Your proposal is acceptable. A statement that since the submission of the application no new relevant safety information was found could also be acceptable, if appropriate.*

Meeting Discussion: None.

**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *Not applicable.*

Meeting Discussion: None.

**9. SAPs for Phase 3 Studies**

**Does the Agency have any comments on the SAP for the pivotal Phase 3 Study 1883-301-013?**

*FDA Response:* *No.*

Meeting Discussion: None.

**10. 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:* *Your proposal is acceptable.*

Meeting Discussion: None.

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

*FDA Response:* *Your proposed subgroups are acceptable. We recommend that the same subgroups be performed for the individual studies.*

Meeting Discussion: None.

**c. Does the Agency have any additional comments on the proposed analysis plans for the ISS and ISE?**

*FDA Response:* *No.*

Meeting Discussion: None.

**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *Not applicable.*

Meeting Discussion: None.

**11. eCRFs and Narratives**

**Does the Agency agree with the proposed eCRFs and narratives to include in the NDA?**
**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *Agree.*

Meeting Discussion: None.

**12. Datasets and Data Standards**

**a. Does the Agency agree with Allergan's plan to provide all datasets, corresponding documentation, and annotated eCRFs in CDISC format for the 2 pivotal Phase 3 studies (Studies 1883-301-013 and 1883-302-013), the ISS/ISE, and 2 of the Phase 2 studies (199201-009 and 199201-010) in the proposed NDA?**

*FDA Response:* *Agree. See response to Question 2 for additional input.*

Meeting Discussion: None.

**b. Does the Agency agree with Allergan's plan to provide all datasets, corresponding documentation, and annotated eCRFs in legacy format for the Phase 2 study 199201-007 in the proposed NDA?**

*FDA Response:* *Agree.*

Meeting Discussion: None.

**c. Does the Agency agree with Allergan's plan to submit key SAS programs for the pivotal studies in the proposed NDA?**
**If the Agency does not agree, please provide any recommendations.**

*FDA Response*: *Agree.*

Meeting Discussion: None.

**13. 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 1883-301-013 and 1883-302-013?**

**If the Agency does not agree, please provide any recommendations.**

*FDA Response:* *Agree.*

Meeting Discussion: None.

**MULTIDISCIPLINARY**

**14. Other Points**

**a. Based on the information 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:* *No.*

Meeting Discussion: None.

**b. Are there any other points that the Agency feels are important to convey to Allergan regarding the planned pilocarpine HCl ophthalmic solution NDA?**

*FDA Response:* It is expected that the marketing application will provide antimicrobial effectiveness testing data that demonstrate the antimicrobial efficacy of the drug product formulated with preservative (BAK) at or below the minimum specified concentration at release or stability (whichever is lower). Please refer to the Agency's 1994 guidance document Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (https://www.fda.gov/files/Guidance-for-Industry-for-the-Submission-Documentation-for-Sterilization-Process-Validation-in-Applications-for-Human-and-Veterinary-Drug-Products.pdf).

Meeting Discussion: None.

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

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/s/

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WILEY A CHAMBERS
12/16/2019 02:36:07 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122483

**MEETING MINUTES**

Allergan, Inc.
Attention: Ms. Jeanne Quigg
Director, Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612

Dear Ms. Quigg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AGN-190584 (pilocarpine hydrochloride ophthalmic solution). We also refer to the teleconference between representatives of your firm and the FDA on November 30, 2018. The purpose of the meeting was to discuss the development of AGN-190584 for the treatment of presbyopia.

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 Diana Willard, Chief, Project Management Staff at (301) 796-0833.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | End-of-Phase 2 |
| **Meeting Date and Time:** | November 30, 2018 from 10:00 AM to 11:00 AM |
| **Meeting Location:** | Teleconference |
| **Application Number:** | IND 122483 |
| **Product Name:** | AGN-190584 (pilocarpine hydrochloride ophthalmic solution) |
| **Indication:** | Treatment of presbyopia |
| **Sponsor Name:** | Allergan, Inc. |
| **Meeting Chair:** | Wiley A. Chambers, MD |
| **Meeting Recorder:** | Eithu Z. Lwin, PharmD |

## FDA ATTENDEES

Wiley A. Chambers, MD, Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, MD, Clinical Team Leader, DTOP
Rhea Lloyd, MD, Clinical Reviewer, DTOP
Sonal Wadhwa, MD, Clinical Reviewer, DTOP
Aaron Ruhland, PhD, Pharmacology/Toxicology Reviewer, DTOP
Chunchun Zhang, PhD, Product Quality Team Leader, Office of Product Quality (OPQ)/New Drug Products Branch III (NDPB III)
Milton Sloan, PhD, Product Quality Reviewer, OPQ/NDPB III
Solomon Chefo, PhD, Statistical Reviewer, OB/DBIV
Wen-Hung Chen, PhD, Clinical Outcomes Assessment Team Leader
Eithu Lwin, PharmD, Regulatory Health Project Manager, DTOP

## SPONSOR ATTENDEES

Paul Stone, PhD, Vice President, Regulatory Affairs
Jeanne Quigg, MBA, RAC, Director, Regulatory Affairs
Tiffanie Yu, MS, Senior Analyst, Regulatory Affairs
Michael Robinson, MD, Vice President, Clinical Development
Haixia Liu, MD, PhD, Director, Clinical Development
Joanna Campbell, PhD, Executive Director, Health Economics Outcomes Research
Elaheh Shirneshan, PhD, Manager, Health Economics Outcomes Research
Anu Gore, PhD, Director, Small Molecule Product Development
Jaya Giyanani, MS, Senior Scientist, Small Molecule Product Development
Grace Le, MD, MHScExecutive Medical Director, Global Patient Safety & Epidemiology

## BACKGROUND

Allergan, Inc. is developing AGN-190584 (pilocarpine hydrochloride ophthalmic solution) for the treatment of presbyopia. Allergan submitted a meeting request on August 10, 2018, requesting a Type B, End-of-Phase 2 meeting to discuss the CMC, nonclinical, clinical, and regulatory topics to support the Phase 3 program and eventual NDA submission under the 505(b)(2) pathway for AGN-190584 for the treatment of presbyopia. A Meeting Request Granted letter was issued on August 21, 2018, granting a meeting for November 30, 2018. The Division issued Preliminary Comments on November 20, 2018, in response to the questions posted in the September 17, 2018, Briefing Package. On November 28, 2018, Allergan emailed their responses to the FDA preliminary responses and stated that further discussion is needed on Questions 9 and 12.

## DISCUSSION

For the purposes of these minutes, the questions posted in the briefing document are in **bold** format, FDA preliminary responses are in *italics*, Allergan responses provided in the November 28, 2018, email are in ***bold italics***, and the meeting discussions are in normal font.

### Impurities

1. **Does the Agency agree with Allergan's proposed shelf life specifications for pilocarpine impurities to support Phase 3 and commercial use? If the Agency does not agree, please provide any recommendations.**

   *FDA Response: The proposed specifications seem reasonable at this stage of development. For a NDA submission, additional tests and/or tightening of the specification may be required. Refer to response to Question 3 for further recommendations.*

   Meeting Discussion: None.

### Nonclinical Data Package for NDA Submission

2. **The planned Allergan commercial product will have a pilocarpine concentration of 1.25%. Commercially available pilocarpine eye drops contain concentrations of pilocarpine of up to 4%. Allergan plans to submit a NDA under the 505(b)(2) pathway and believes that no additional nonclinical studies are necessary to support registration.**

   **Does the Agency agree? If the Agency does not agree, please provide any recommendations.**

   *FDA Response: We agree.*

   Meeting Discussion: None.

### Toxicological Characterization of Degradants

3. **Does the Agency agree that the available data, including the results of the 6-month chronic ocular toxicity study, are sufficient to support the proposed specifications for**

[redacted](b) (4)**? If the Agency does not agree, please provide any recommendations.**

*FDA Response: The final study report for the 6-month chronic ocular toxicity study has not yet been submitted for review. The study design and scope appear sufficient to support the proposed specifications. Upon review, if no toxicity is found to be associated with the impurities at the concentrations stated in the briefing document, then the study may be sufficient to qualify the impurities at the specifications proposed. In the NDA application, please provide discussion of this justification.*

Meeting Discussion: None.

**Planned Pharmacokinetic Assessments**

4. **Does the Agency agree that the proposed PK plan is sufficient to support the registration of pilocarpine HCl ophthalmic solution 1.25% for the treatment of presbyopia? If the Agency does not agree, please provide any recommendations.**

   *FDA Response: We agree with your proposed plan to characterize the systemic PK following administration of the proposed pilocarpine ophthalmic solution 1.25% given once daily in a subset of approximately 24 presbyopia patients in one of your proposed Phase 3 studies. The proposed PK sampling time points are also acceptable.*

   Meeting Discussion: None.

**Clinical Study Duration and Dose Regimen**

5. **Does the Agency agree that two Phase 3 pivotal studies of 30-day duration are adequate to support a NDA submission for pilocarpine hydrochloride ophthalmic solution 1.25% as a bilateral, once-daily treatment for presbyopia? If the Agency does not agree, please provide any recommendations.**

   *FDA Response: Agree.*

   Meeting Discussion: None.

**Primary Efficacy Endpoint**

6. **Does the Agency agree with the primary efficacy endpoint proposed for the Phase 3 studies? If the Agency does not agree, please provide any recommendations.**

   *FDA Response: Yes, the proposed primary efficacy endpoint is acceptable.*

   Meeting Discussion: None.

**Statistical Analysis Method for Primary Efficacy Endpoint**

7. **Does the Agency agree with the analysis method for the proposed primary endpoint for the Phase 3 studies? If the Agency does not agree, please provide any recommendations.**

*FDA Response: Agree. In addition to the chi-square test for the primary efficacy endpoint, please provide the treatment difference in proportion and the corresponding 95% confidence interval estimates.*

Meeting Discussion: None.

**Secondary Efficacy Endpoints and Analysis Methods**

**8. Allergan is proposing two key secondary efficacy endpoints and five lower-level secondary endpoints, some of which are gated to additional related secondary efficacy endpoints.**

**a) Does the Agency agree with the secondary efficacy endpoints for the Phase 3 studies? If the Agency does not agree, please provide any recommendations.**

*FDA Response: The proposed key secondary efficacy endpoints and lower-level secondary efficacy endpoints for the Phase 3 studies are acceptable* (b) (4) *. You would have to establish the clinical significance of the endpoint.*

Meeting Discussion: None.

**b) Does the Agency agree with the proposed statistical analysis strategy for the secondary efficacy endpoints for the Phase 3 studies? If the Agency does not agree, please provide any recommendations.**

*FDA Response: Agree. We have the following comments for your consideration:*

*i) You proposed MMRM models to analyze all continuous secondary efficacy variables (excluding PRO-related variables). Your proposed MMRM models include treatment group, age group, baseline DCNVA severity, iris color, and emmetropes/non-emmetropes (and baseline values for non-AUC related endpoints) and use an unstructured covariance structure to account for the within subject correlation. However, without including VISIT and the interaction term of VISIT by TREATMENT as a fixed effect in your model, it is not clear how the analysis would be conducted for the secondary endpoints evaluated at a given study visit. Please clarify and provide your sample SAS codes for the analysis.*

*Furthermore, since the MMRM model relies on the missing at random (MAR) assumption for missing data and the MAR assumption cannot be verified based on observed data, we recommend that you conduct detailed sensitivity analyses to evaluate the robustness of the efficacy results.*

*ii) You proposed to test the five lower level secondary efficacy variables by splitting the α-level if the primary and the two key secondary efficacy variables are statistically significant. We have no objection with your approach; however, you should pre-specify how you plan to split the α-level to test these variables (e.g. Bonferroni). Also, you should clarify the testing strategy for the last two PRO-related lower-level secondary efficacy variables as your testing strategy in Figure 14-2 is not clear.*

Meeting Discussion: None.

**Label Warning – Low Illumination Conditions**

9. **Does the Agency agree that (b) (4) (b) (4) (b) (4) the label warning and precaution associated with night driving and hazardous occupations in poor illumination (b) (4) If the Agency does not agree, please provide any recommendations on the type of data that would be needed to (b) (4).**

*FDA Response: Labeling is a review issue that requires review of a complete application to address. It is the Agency's expectation that labeling for your proposed product would include this warning associated with night driving and hazardous occupations in poor illumination. If you believe that this language does not apply to your product, data to support its exclusion should be submitted with your application.*

***Allergan Response: The Phase 3 studies will be collecting near, intermediate, and distance visual acuity and contrast sensitivity data under low illumination conditions. Could the Agency provide recommendations on the type of additional evidence that may be required to support (b) (4) if the Phase 3 visual acuity and contrast sensitivity data is not deemed to be sufficient?***

Meeting Discussion: (b) (4) The Agency responded that this general warning applies to products that decrease pupil size because there will be less light entering the eyes because of decreased pupil size. The Agency would be willing to consider modifying the warning language if there is data to support this modification. (b) (4). The Agency agreed to Allergan's proposal to submit a meeting request to discuss the proposed study design on low illumination evaluations such as a simulated nighttime driving test.

**Subgroup Analyses**

10. **Does the Agency agree with Allergan's plan to only perform subpopulation analyses on the pooled Phase 3 data? If the Agency does not agree, please provide any recommendations.**

*FDA Response: In addition to the pooled data, we recommend that subgroup analyses also be performed for the individual studies.*

Meeting Discussion: None.

**Presbyopia Population Exposure**

**11. Does the Agency agree that this sample size is sufficient to establish the safety and efficacy of the pilocarpine HCl ophthalmic solution 1.25% as a treatment for presbyopia? If the Agency does not agree, please provide any recommendations.**

*FDA Response: Agree. However, the 20% dropout rate assumed in your sample size calculation is high and would not be acceptable in such a short-term study. Thus, we recommend that in the protocol you specify measures to minimize missing data and to encourage patients who discontinue study drug early to stay in the study for the efficacy and safety assessments at Day 30.*

Meeting Discussion: None.

**Patient Reported Outcomes**

**12. Allergan plans to include the NVPTQ and PICQ PROs in the upcoming Phase 3 studies to support efficacy endpoints and generate data on the patient-reported benefits of treatment with pilocarpine HCl ophthalmic solution 1.25% in patients with presbyopia.**

**a) Does the Agency agree that mesopic NVPTQ Performance domain (NVPTQ Items 1, 4, 7, and 10) represents a well-defined, valid measure of vision-related reading ability in presbyopia? If the Agency does not agree, please provide any recommendations.**

*FDA Response: The NVPTQ excludes reading using electronic devices (i.e., cellphone, tablet, and laptop) which does not reflect our real-world reading activities. We recommend reading using electronic devices be included in NVPTQ in phase 2 studies for use as an exploratory endpoint. Reading ability using electronic devices may be excluded if the data suggest that it is highly associated with reading ability with paper media.*

*We have concerns that the NVPTQ may not have concurrent validity or be sensitive enough to detect change in reading ability. As the results in Study 199201-010 showed that "moderately better" group also did not reach statistical significance versus the "no change" group, with small effect sizes observed. Only the" complete improvement/far better" rating group in both performance and satisfaction domains reached statistical significance and moderate effect sizes. We recommend that you conduct further quantitative evaluation of NVPTQ (after revision if necessary).*

***Allergan Response:***

***Electronic tasks***

***Allergan appreciates the Agency's feedback and recognizes the relevance of electronic-based tasks in society today. Three electronic reading tasks were included in the original version of the NVPTQ for evaluation during cognitive debriefing. These tasks included: reading a text message on an iPhone; reading a book excerpt on an iPad; and reading a credit card statement on a MacBook Pro computer. Ultimately, these tasks were not carried forward due to several concerns identified by Presbyopia***

***patients. For example, patients commented that the tasks were unrealistic (did not represent their experience with electronic media) as the tasks did not allow patients to adjust the screen luminance, contrast or font size – all of which patients would do in real life to increase their ability to see electronic text.***

***Therefore, the decision was made to focus the NVPTQ on assessing reading ability through the completion of paper-based reading tasks. The tasks included in the NVPTQ represent tasks that were identified in the qualitative phase as important and relevant to Presbyopia sufferers and facilitate assessment of the most commonly reported and most bothersome impacts of Presbyopia.***

***Allergan does not plan to include electronic based tasks, even for exploratory purposes in the upcoming Phase 3 program; given the strong support from Presbyopia sufferers regarding the relevance of paper-based tasks in their daily lives, the qualitative evidence suggesting difficulties with the device reading tasks, and the time and logistical challenges to implement electronic reading tasks in these studies. Allergan acknowledges that the use of electronic devices to complete everyday reading tasks will only continue to increase over time and plans to explore this separately for future programs.***

***Concurrent validity***

***Allergan acknowledges that current evidence for concurrent validity based on correlations with Near Vision Subscale of NEI VFQ-25 is not strong. This is not unexpected as:***

***(a) patients were instructed to answer the NEI VFQ-25 questions as if they were wearing glasses, or contact lenses, while the NVPTQ was conducted under mesopic conditions without additional near vision correction;***

***(b) the NEI VFQ-25 does not specify a recall period, while the NVPTQ effectively has an immediate recall period; and***

***(c) self-reported difficulty with a broad range of near-vision activities as measured by the Near Vision Subscale may be measuring a different construct from self-rated performance and satisfaction with the ability to read the specific text examples measured by the NVPTQ.***

***Stronger correlations were observed between the change from baseline in NVPTQ Performance and Satisfaction scores and Patient Global Impression of Change (PGIC) question.***

***It is important to consider all of the psychometric results regarding validity of the measure. Specifically, strong known-groups validity for the NVPTQ Performance score was demonstrated (Table 10 in the psychometric validation report provided in Appendix 3 in the briefing package).***

***Allergan is planning further quantitative evaluation of concurrent validity, as well as sensitivity of the NVPTQ Performance score in the upcoming Phase 3 studies. In the Phase 3 studies, in addition to the PGIC question, we have included a Patient Global***

***Impression of Status (PGIS) question, which we consider to be an appropriate measure for assessing validity and responsiveness of the NVPTQ Performance score.***

***Sensitivity***

***With respect to sensitivity, we consider our instrument will be sensitive enough to show the level of change that is expected, given the size of our anticipated treatment effect.***

***Based on this information Allergan plans to use the NVPTQ in the Phase 3 studies, does the Agency have any additional comments?***

Meeting Discussion: The Agency responded reading ability using electronic devices is very important and that it may not worth pursuing without it. The Agency recommended using electronic devices that are realistic to better reflect patients' experience with electronic devices in real life. The Agency further stated that the PICQ is about coping domains and the ability to adjust the screen luminance, contrast or font size to improve patients' ability to read electronic text better is a coping method.

The Agency stated that the correlation for the concurrent validity seemed low and that it was not in a range that they usually saw in other patient-reported outcome measures. Allergan clarified that they expected the correlation to be low because NVPTQ and NEI VFQ-25 were not exactly measuring near-vision activities in the same way.

Regarding sensitivity to detect change in Phase 2 trial, the Agency stated the only group that showed statistically significant difference from the no change group was the complete improvement/far better group. There was no difference between the moderately better, slightly better, and no change groups. The Agency commented that this result suggested the NVPTQ may be only sensitive to a very large improvement in reading ability.

The Agency stated that there may be too many tasks in NVPTQ and maybe Allergan could consider reducing the number of tasks so that make sure that patients are not too fatigued. The Agency asked what happened to the patient's score if the patient moved the test reading material back and forth, not keeping the required 40-centimeter distance. The Agency also asked if squinting affects the test score since patients are told not to squint. Allergan clarified that the patients do not hold the test reading material themselves and that study procedure does not allow patients to move their head or body, such as leaning forward. In addition, Allergan responded that squinting does not change the reported score. The Agency raised the concern that if the patient squints, it may have an effect on the reading ability. The Agency requested Allergan to provide detailed analysis on the potential impact of squinting.

**b) Does the Agency agree that the mesopic NVPTQ Satisfaction domain (NVPTQ Items 3, 6, 9 and 12) represents a well-defined, valid measure of patient satisfaction with the vision-related reading ability in presbyopia? If the Agency does not agree, please provide any recommendations.**

*FDA Response: It appears that improvement in reading ability is highly associated with satisfaction with reading ability. We recommend that you provide evidence that patient's*

*satisfaction to reading ability adds supplemental information that is not already captured by improvement in reading ability.*

***Allergan Response:** Based on the correlation between the two domain scores, improvement in reading ability is highly associated with satisfaction with reading ability (Spearman correlations were 0.84 in study 199201-010 and 0.83 in study 199201-009, at baseline). Allergan believes that our qualitative research demonstrates that improvement in reading ability and satisfaction with reading ability are regarded by patients as conceptually distinct and both are important to the patient experience of their condition and functioning in their daily life.*

***During qualitative interviews, patients did take more factors than reading ability into account when assessing satisfaction, such as use of coping mechanisms (e.g., squinting, reading glasses) and impacts experienced (e.g., headaches). In contrast, patients' interpretation of "ability to read" was mainly focused on their ability to see the words clearly on the paper, and coping/impacts were not discussed as much when interpreting these answers. It is possible for patient satisfaction with reading to decrease while the ability to read remains constant if there is increased reliance on compensatory coping mechanisms, or experience of negative impacts.***

***Please see Table 1 for sample quotes in this regard:***

**Table 1: Patient quotes from qualitative interviews supporting supplemental information captured by the Satisfaction domain**

| Participant ID | Interpretation of "Ability to read" | Interpretation of "Satisfaction with ability to read" |
|---|---|---|
| (b) (6) | I'm thinking uh, can you **see it clearly** or is it **fuzzy** or, or anything like that or if it's too **dim** or something like that, it's more than I was, the question to me is what they're asking. | I'm going to pick neither, dissatisfied, dissatisfied or satisfied.<br><br>*Q: Okay, why would you choose that?*<br><br>A: Um, because it wasn't really hard for me to read, I can see it, but the **lighting, I think could have been better**…You know, so, but it, it's, it didn't really affect one way or the other really, course I really don't know that because the light, you know, I mean we haven't really tried it with the light on, so, I'm assuming it wouldn't be much of a difference.<br><br>**Q: Okay. Um, if you were to choose very dissatisfied what would that mean?**<br><br>A: Um, basically that you had a **very hard time reading it cause you were squinting** and you just couldn't see it very well. |

| | | |
|---|---|---|
| (b) (6) | So the for me the question about reading the text in the book is um, how well I'm able to, how **well I'm able to actually read it**, not necessarily understand it… but um**, how well I'd be able to see** and read it. | Um, I would say for me **very dissatisfied** just because um, I get my migraines from if I don't wear my glasses when I'm reading so **if I was to continue reading a book uh like that and the distance um, I would end up with a huge migraine** and have to take medication for that so, yeah. |

***Based on this information, does the Agency have any additional comments?***

Meeting Discussion: The Agency noted that the correlation between the reading ability items and the satisfactions items are very high, more than 0.8. The Agency also acknowledged the patient quotes included in Allergan's responses to demonstrate that satisfaction is more than reading ability. The Agency recommended that in order to demonstrate that satisfaction is more than reading ability, it is necessary to show that patient satisfaction moves independently of reading. One of the analyses could be to show higher patient satisfaction in treatment arm than in control arm while controlling the reading ability.

**c) Does the agency agree that the PICQ Coping domain (PICQ Items 1-8, 12-15) represents a well-defined, valid measure of presbyopia coping mechanisms? If the Agency does not agree, please provide any recommendations.**

*FDA Response: We are concerned about the item redundancy. It is not clear how the coping and impact domains of PICQ were created and how the items were identified as assessing one or the other. Although the result of confirmatory factor analysis showed acceptable model fit statistics, the interpretability of the model needs to be discussed and clarified further. We recommend that you provide detailed information regarding the determination of the domains and their items, as well as the detailed results of the confirmatory factor analysis. We also recommend that you conduct an exploratory factor analysis to generate information for potential alternative models.*

*We have concerns that the PICQ may not have concurrent validity or be sensitive enough to detect change in reading ability. As the results in Study 199201-010 showed that "moderately better" group also did not reach statistical significance versus the "no change" group, with small effect sizes observed. Only the" complete improvement/far better" rating group in both performance and satisfaction domains reached statistical significance and moderate effect sizes. We recommend that you conduct further quantitative evaluation of PICQ (after revision if necessary)*

***Allergan Response:***

***Item redundancy***

***Based on the totality of evidence from the qualitative and quantitative research, Allergan believes that the 20 items retained in the PICQ are important and relevant to presbyopic patients and does not plan to revise the PICQ.***

***During the psychometric evaluation of the PICQ, seven items were flagged as candidates for assessment of item redundancy and potential removal from the PICQ. After consideration of the qualitative evidence, quantitative evidence, and clinician input; three items (4, 20, and 23) were eliminated from the questionnaire; while items 1,2, 9 and 11 were retained due to robust evidence supporting their content validity. These items will be monitored further in the confirmatory analysis of the PICQ in the upcoming phase 3 studies. Table 2 provides a summary of the evaluation of item redundancy and final decisions, which was previously submitted in Appendix 3 of the briefing package.***

**Table 2: Evaluation of Item Redundancy in the PICQ**

| **Items Retained** | | |
|---|---|---|
| **Concept (item number*)** | **Results** | **Rationale** |
| Need aid for normal-sized text (Item 1)<br><br>Need aid for small-sized text (Item 2) | A ceiling effect was observed for Item 1 (over half of responses were at the ceiling value of "all of the time.")<br><br>Items 1 and 2 showed high inter-item correlation with one another. | Ceiling effect expected, as inclusion criteria for the study required at least +1.00 magnitude for reading; therefore, both items were retained as they were highly endorsed by both patients and physicians as relevant. |
| Switching from near-vision to far-vision glasses (Item 9) | 41.1% of subjects reported they did not use correction for distance vision. | This can be accounted for because all subjects were emmetropes that did not use correction for distance vision. This item was retained in the Coping score as it is relevant to the broader presbyopic patient population that will be in the Phase 3 studies, despite not being as relevant to the subjects in the Phase 2 studies. |
| Difficulty working with small objects due to problems seeing up close (Item 11) | Was not answered by 25% of subjects. | This item captures some of the non-reading small object tasks that patients discussed during concept elicitation interviews. At least 65% of patients (n=20) during Concept Elicitation interviews discussed difficulty with some sort of small task and this item was intended as a "catch-all" to capture some of these impacts. |
| **Items Eliminated** | | |
| **Concept (item number*)** | **Results** | **Rationale** |
| [redacted] (b) (4) | | |


* Item numbers reflect pre-validation version

***Factor structure***

***Allergan considers the current PICQ factor structure to be simple, easily interpretable, and supported by both the qualitative research and quantitative evidence, and that exploratory factor analysis (EFA) is not needed.***

***While multiple factor structures could have been posited, the conceptual framework model was ultimately chosen as it is supported by the qualitative research conducted on the PICQ. Results of confirmatory factor structure (CFA) were provided in the response to the Agency's November 19, 2018 Information Request (SN 0024) and further support the appropriateness of the current factor structure.***

***The current factor structure of PICQ consists of two primary domains: Impact (items 9-11 and 16-20) representing impacts of presbyopia, and Coping (items 1-8 and 12-15) representing coping behaviors to counteract Presbyopia impacts. These two domains are based on the conceptual framework developed for the PICQ, in accordance with the FDA Final Guidance for Industry PRO Measures:***

- ***A preliminary conceptual framework was developed for PICQ based on the findings from the literature review. Specifically, each symptom or impact concept that was discussed in the literature, and/or was part of an item in an existing relevant vision-related PRO instrument, was reviewed by the study team and included or excluded from the preliminary conceptual framework.***
- ***The preliminary conceptual framework was revised following concept elicitation interviews with presbyopic patients. If a concept was mentioned in the literature, but was not reported by patients during interviews, the concept was excluded from the revised conceptual framework and therefore could not be a potential item in the PICQ.***
    - ***During concept elicitation, patients frequently mentioned numerous coping behaviors used to mitigate the effects of presbyopia (e.g., use of spectacles, squinting, holding materials farther out to read), in addition to general impacts of presbyopia. Therefore, the conceptual framework was modified to include a new, separate concept of "coping mechanisms".***

- ***The revised conceptual framework assisted in the item generation for the PRO instrument development. Following the cognitive interviews, conceptual framework was revised again. Concepts were replaced with actual item wording and any items that were added or removed based on the results of the cognitive interviews were reflected in the revised framework (see Appendix 1).***

***Concurrent validity and sensitivity***

***Please see our response to the Agency's preliminary comments on Question 12a as the same approach will be taken with respect to further evaluation of the PICQ.***

Meeting Discussion: The Agency stated that #9 and #11 do not respond to redundancy. There is redundancy in #1 and #2 as they are locally dependent. If a patient does not have difficulty with small size text then that patient would not have difficulty with normal size text, and if a patient has difficulty with normal size text then that patient would also have difficulty with small size text. Basically, ability to read small size text cannot be better than the ability to read normal size text and therefore their answers are dependent. Because of the dependency, the reliability of the PICQ is inflated. PICQ may not be as reliable as its reliability coefficient. There are other redundant item pairs such as item 13 and items 1 and 2, and items 6 and 8.

Regarding PICQ Factor Structure, the Agency commented that some impact items may be coping items, such as Question #9. Allergan clarified that Question #9 was more about being independent, rather than social relationship, and therefore it was considered an impact item.

The Agency further commented that we should not only look at the model goodness of fit indices, we should more importantly examine whether the model is interpretable. Agency acknowledged that the model goodness fit of indices from the confirmatory factor analysis showed a good model fit for the proposed conceptual framework. The Agency suggested that the acceptable indices values may be inflated by the locally dependent item pairs. The Agency suggested to conduct an exploratory factor analysis to see whether a more interpretable model may be identified.

The Agency also raised concern regarding the recall period of the past 7 days for the PICQ. The Agency noted that previous work on how accurately people could remember, suggested that people could not remember accurately over 4 hours. Allergan will reassess the appropriate length of recall.

**d) Does the agency agree that the PICQ Impact domain (PICQ Items 9-11, 16-20) represents a well-defined, valid measure of presbyopia impacts? If the Agency does not agree, please provide any recommendations.**

*FDA Response: Please see our response to Question 12c.*

***Allergan Response: Please see our response to Question 12c.***

***Based on this information Allergan plans to use the PICQ in the Phase 3 studies, does the Agency have any additional comments?***

Meeting Discussion: Please see meeting discussion to Question 12c.

**Statistical Analysis Plan**

**13. Does the Agency have any additional comments about the Statistical Analysis Plan in Appendix 7?**

*FDA Response: Not at this time.*

Meeting Discussion: None.

**Phase 3 Study Design**

**14. Does the Agency have any other comments on the design of the proposed Phase 3 studies such as the inclusion/exclusion criteria and safety assessments (Appendix 1)?**

*FDA Response: Not at this time.*

Meeting Discussion: None.

**Regulatory Pathway**

**15. Does the Agency agree that the future NDA for pilocarpine as a treatment for presbyopia using the 505(b)(2) regulatory path is appropriate? If the Agency does not agree, please provide any recommendations.**

*FDA Response: We agree. Please note that impurity specifications may not be based on a study's summary description in an FDA discipline NDA review for which you do not have right of reference (e.g.,* (b) (4) *).*

Meeting Discussion: None.

**Pilocarpine Name in Labeling**

**16. Does the Agency agree that** (b) (4) (b) (4) (b) (4) **If the Agency does not agree, please provide any recommendations.**

*FDA Response: No.* (b) (4) (b) (4)

Meeting Discussion: None.

**Target Product Profile (TPP)**

**17. A draft TPP for pilocarpine HCl ophthalmic solution 1.25% is provided in Appendix 8 to facilitate a structured dialogue with the Agency to communicate Allergan's desired**

**label claims and to reach an understanding of the FDA's thinking on the development program.**

**a) Does the Agency agree with the presentation of the proposed primary efficacy endpoint for the Phase 3 pivotal studies in Section 14 of the TPP (see Question 6)? If the Agency does not agree, please provide any recommendations.**

*FDA Response: Labeling is a review issue that requires review of a complete application to address. Comments on specific labeling is premature.*

Meeting Discussion: None.

**b) Does the Agency agree that the pre-defined key secondary efficacy endpoints and the selected additional pre-defined efficacy secondary endpoints can be described in the labeling if they are positive (see Question 8). If the Agency does not agree, please provide any recommendations.**

*FDA Response: Labeling is a review issue that requires review of a complete application to address. Comments on specific labeling is premature.*

Meeting Discussion: None.

**c) Does the Agency have any other comments on the TPP?**

*FDA Response: No.*

Meeting Discussion: None.

**Pediatric Study Plan Waiver**

**18. Does the Agency agree that a full waiver from the requirement to conduct clinical studies in all age groups of the pediatric population is appropriate? If the Agency does not agree, please provide any recommendations.**

*FDA Response: A Pediatric Plan should be submitted within 60 days of this End of Phase 2 meeting. The Pediatric Plan should describe your rationale for requesting a full waiver. We will comment on your plan after it is submitted.*

Meeting Discussion: None.

**Study Data Standardization Plan**

**19. Does the Agency agree with the Study Data Standardization Plan (SDSP) provided in Appendix 9? If the Agency does not agree, please provide any recommendations.**

*FDA Response: Agree.*

Meeting Discussion: None.

## ADDITIONAL COMMENTS

*You should provide the user manual for all PRO instruments that will be used in your Phase 3 trials.*

## PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

## DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data

requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

## LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For

more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

## SUBMISSION FORMAT REQUIREMENTS

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

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

## SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

## 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

| **List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature** | |
|---|---|
| **Source of information (e.g., published literature, name of listed drug)** | **Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)** |
| *1. Example: Published literature* | *Nonclinical toxicology* |
| *2. Example: NDA XXXXXX "TRADENAME"* | *Previous finding of effectiveness for indication A* |
| *3. Example: NDA YYYYYY "TRADENAME"* | *Previous finding of safety for Carcinogenicity, labeling section B* |
| *4.* | |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

## OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for

CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

**NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

**ISSUES REQUIRING FURTHER DISCUSSION**
None.

**ACTION ITEMS**
- Allergan to respond to the Agency's verbal information request regarding patients' response to squinting in NVPTQ.

- The Agency will issue Meeting Minutes within 30 days of the meeting.

**ATTACHMENTS AND HANDOUTS**
- Appendix 1 – Final Conceptual Framework for PICQ

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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WILEY A CHAMBERS
12/14/2018