CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215092Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 111518

MEETING MINUTES

Santen Incorporated
Attention: Raul Brena, RAC
Global Regulatory Affairs Manager
6401 Hollis Street, Suite 125
Emeryville, CA 94608

Dear Mr. Brena:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DE-117 (omidenepag isopropyl ophthalmic solution).

We also refer to the teleconference between representatives of your firm and the FDA on June 10, 2020. The purpose of the meeting was to discuss the clinical data package and submission strategy of your planned New Drug Application.

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

If you have any questions, call Lois Almoza, M.S., Senior Regulatory Health Project Manager at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 10, 2020 from 12:30pm – 1:30pm (EST)
Meeting Location:	Teleconference
Application Number:	111518
Product Name:	DE-117 (omidenepag isopropyl ophthalmic solution)
Indication:	intraocular pressure lowering in open-angle glaucoma or ocular hypertension
Sponsor Name:	Santen Incorporated
Regulatory Pathway:	505(b)(1) of the Food, Drug, and Cosmetics Act
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Lois Almoza, M.S.

FDA ATTENDEES

Wiley A. Chambers, M.D., Acting Director, Division of Ophthalmology (DO)
William M. Boyd, M.D., Clinical Team Leader, DO
Martin Nevitt, M.D., Clinical Reviewer, DO
David Summer, M.D., Clinical Reviewer, DO
Guoxing Soon, Ph.D., Statistical Team Leader, Office of Biometrics (OB)
Abel Eshete, Ph.D., Statistical Reviewer, OB
Lois Almoza, M.S., Senior Regulatory Health Project Manager, Division of Regulatory Operations for Specialty Medicine

SPONSOR ATTENDEES

Lili Arabshahi, MBA, Ph.D., Project Manager, Global Product Development
Raul Brena, RAC, Manager, Global Regulatory Affairs
Franz Buchholzer, Ph.D., Vice-President of Global Regulatory Affairs
Almira Chabi, M.D., Vice-President of Glaucoma and Neuroprotection Therapeutic Area Strategy
Julia Chen, Ph.D., Senior Regulatory Affairs Specialist
Chun-Jung Chu, Ph.D., Associate Director, Pharmaceutical Development
Phillip Dinh, Ph.D., Director, Biostatistics, Global Data Science
Reza Haque, M.D., Ph.D., Senior Vice President, Head of Global Biomedical Strategy & Research
Schonmei Lee, M.D., Associate Director, Safety Vigilance Risk Management
Fenghe Lu, M.D., Ph.D., Director, Clinical Sciences, Glaucoma and Neuroprotection Therapeutic Area

Noriko Odani Kawabata, Ph.D., Director, Development Lead, Glaucoma and Neuroprotection Therapeutic Area
Peter Sallstig, M.D., MBA, Senior Vice President, Global Head Product Development
Usha Srinivasan, M.S., RAC, Senior Director, Global Regulatory Affairs
Lening Zhang, Ph.D., Associate Director, Biostatistics, Global Data Science

BACKGROUND

According to Santen Incorporated (Santen), a New Drug Application (NDA) for DE-117, omidenepag isopropyl ophthalmic solution, is planned to be submitted to FDA for review as a 505(b)(1). The proposed clinical package for the DE-117 NDA filing will include one Phase 1 human pharmacokinetics (PK) study, four Phase 2 dose-finding studies, one dose frequency study, two US Phase 3 pivotal studies (011710IN and 011709IN) and one Asian Phase 3 pivotal study (01171505).

Santen submitted the Briefing package on 24 April 2020 for the pre-NDA meeting for DE-117 granted for June 10, 2020 and received the FDA preliminary comments on June 4, 2020 via e-mail. After review of the preliminary comments, Santen decided to address and clarify FDA's responses to questions 1, 3, and 4 and offer further details to the composition of the clinical studies for the NDA and the plan for the 120-Day safety update. On June 16, 2020, Santen submitted the PowerPoint presentation discussed during the teleconference to the application on file.

DISCUSSION

Following, in **bold font**, are the questions in the April 24, 2020, Meeting Package. The FDA responses to these questions are in *italic* font. Discussions that took place during the June 10, 2020, teleconference are in regular font.

Clinical

1. **Does the Agency agree that the data from the Asian Phase 3 study (01171505) and the US Phase 3 (011710IN) study will support the efficacy of DE-117 and form the basis for an NDA filing for DE-117?**

FDA Response: *We would expect the application to include the complete study reports for all of the Phase 1, 2 and 3 studies including: the pharmacokinetic study, the Asian Study (01171505) and the two US studies (011709IN and 011710IN). If these studies are adequate and well controlled studies, they would be adequate for NDA filing; approvability of the application is a review issue.*

Meeting Discussion:
Santen agreed to provide the complete study reports for all the Phase 1, 2 and 3 studies including: the pharmacokinetic study, the Asian Study (01171505) and the two US studies (011709IN and 011710IN). Santen discussed the outcome of the clinical studies that were designed as adequate well-controlled studies that would comprise the Phase

3 package of the NDA, specifically, 01171505, 011709IN and 011710IN. Santen indicated that while studies 01171505 and 011710IN met the FDA-specified non-inferiority criteria, study 011709IN failed to do so, nevertheless, the efficacy profile of DE-117 was consistent with that seen in study 011710IN.

The FDA stated that the studies intended to support the NDA appeared to be adequate and well-controlled and that the data package would most likely be fileable, but determination on approvability would be based on review. The FDA urged Santen to submit the NDA as soon as possible.

2. **Does the Agency agree that no pooled ISE analysis is necessary in the DE-117 NDA?**

FDA Response: *Agree.*

Meeting Discussion: None

3. **Does the Agency agree that the proposed data package for the 120-Day Safety update to the NDA will meet the ICH requirement for long-term exposure?**

FDA Response: *The proposed data package for the 120-Day Safety update appears acceptable. You state at the time of the 120-Day safety update, the only new data since the NDA submission will come from the 9-month open-label treatment phase of Study 011709IN. Any additional safety data on the drug product identified from any of the other trials should also be submitted in the 120-Day Safety update.*

Meeting Discussion: Santen stated that there will be new open-label data from study 011709IN for the 120-Day Safety Update and that the CSR will be updated. Santen also provided information about the 3 ongoing studies: (b) (4) and stated that the 120-Day Safety Update will include a summary of data from these studies provided in DSUR format.

The FDA found the Santen's plan for the 120-Day Safety Update acceptable and asked the Santen not to unblind any ongoing studies to support the safety update. The FDA stressed that any new significant safety information will need to be submitted.

Pharmacovigilance

4. **In the 120-Day safety update, the Sponsor is planning on only updating open-label data from the US Phase 3 Study 011709IN in its Clinical Study Report (CSR) and not integrating this updated data into the Integrated Summary of Safety (ISS).**

   Does the Agency agree with this approach for the 120-Day safety update?

FDA Response: *Agree. See response to Q 3.*

Meeting Discussion: None

Regulatory

5. **Does the Agency agree that an Instructions for Use document will not be required for marketing DE-117?**

FDA Response: An Instructions for Use document is not required for submission of your NDA. Labeling is a review issue requiring review of the submitted application in its entirety.

Meeting Discussion: None

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

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
07/06/2020 04:38:57 PM

IND 111518

MEETING PRELIMINARY COMMENTS

Santen Incorporated
Attention: Raul Brena, RAC
Global Regulatory Affairs Manager
6401 Hollis Street
Suite 125
Emeryville, CA 94608

Dear Mr. Brena:

Please refer to your investigational new drug application (PIND) file for DE-117 ophthalmic solution.

We also refer to your April 24, 2019, correspondence, requesting a meeting to discuss obtain preliminary agreement and feedback regarding the content and format of the NDA package and the adequacy of data to support the DE-117 new drug application. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. The official record of this meeting will be the FDA-generated minutes. If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 12, 2019 from 10:00am – 11:00am
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: 111518
Product Name: DE-117 ophthalmic solution
Indication: ocular hypertension or open-angle glaucoma
Sponsor Name: Santen Incorporated

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 12, 2019. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

DISCUSSION

Following, in **bold** font, are the questions in the June 11, 2019, Meeting Package. The FDA responses to these questions are in *italic* font.

Clinical/Biostatistics

1. **Does the agency agree that the proposed data package that will be available at the time of the initial submission is acceptable for NDA filing?**

FDA Response: Yes.

2. **Does the agency agree that the proposed data package that will be available at the time of the Day 120 safety update is acceptable to meet NDA requirements?**

FDA Response: Yes.

Clinical

3. **Protocol 011709IN (Spectrum 3) and 011710IN (Spectrum 4) are two U.S. Phase 3 trials with identical study design for the first 3-month double-masked treatment period, and include the same control comparator, timolol. The only difference between the trials is that the Spectrum 3 study (Protocol 011709IN) continues on after the initial 3 months to an additional 9-month open-label treatment period (during the 9-month period, all subjects receive DE-117). Sponsor is planning to integrate efficacy data from these two U.S. phase 3 trials. These data will be summarized in the Integrated Summary of Efficacy (ISE) with 3 months of double-masked treatment duration.**

   Does the agency agree with this approach for the ISE?

FDA Response: We agree with this approach, provided that the clinical study reports and datasets will also be submitted separately for each study.

Data Management

4. **Does the Agency agree with the proposed plan for the CRF submission?**

FDA Response: Yes

Statistical Programming

5. **Sponsor plans to submit CDISC compliant datasets for all clinical studies except for DE-117 ophthalmic solution (0.003%, 0.01%, and 0.03%) 33-001 study, a legacy study that started and was completed prior to the study**

data standards requirement. The study data for this study will be submitted in the legacy format. See the Study Data Standardization Plan on Section 11 for specific information.

Does the agency agree with this approach?

FDA Response: Yes.

6. **Sponsor plans to provide the data definition files (i.e., annotated CRF, reviewer's guides and define.xml files) for the two U.S. phase 3 trials with timolol control (Protocol 011709IN and 011710IN); however, Sponsor will only submit the datasets for the non-pivotal studies. See the Study Data Standardization Plan on Section 11 for specific information.**

   Does the agency agree with this approach?

FDA Response: We agree with this approach, provided that a define document for the datasets will be submitted for all studies.

7. **Sponsor plans to submit the study data with the medical coding version, and control terminology, used at the time of the conduct of the study; however, we will up-version the coding within the Integrated Summary of Safety (ISS) datasets to be a consistent version for the analysis. See the Study Data Standardization Plan on Section 11 for specific information.**

   Does the agency agree with this approach?

FDA Response: Yes.

8. **For the Clinical Study Reports Appendices section 16.4, in lieu of Subject Profiles or individual subject listings, Sponsor plans to provide CDISC compliant datasets, the data definition files, and the Bioresearch Monitoring Program (BIMO) listings for the two U.S. Phase 3 trials with timolol control (Protocols 011709IN and 011710IN).**

   Does the agency agree with this approach?

FDA Response: Yes.

Pharmacovigilance

9. **Sponsor is planning to split the Integrated Summary of Safety (ISS) between Module 2 and Module 5. The primary discussion and analysis of safety in the Integrated Summary of Safety will be in section 2.7.4, and the appendices and datasets will be placed in section 5.3.5.3. Because the safety profile of DE-117 is relatively straightforward, Sponsor believes the text portion of the ISS will fit within the page restrictions for the clinical summary sections.**

Does the agency agree with this approach for the ISS?

FDA Response: Yes.

10. **Sponsor plans on integrating safety data from only the Phase 3 trials (Protocol 01171505 with Asian population, Protocols 011709IN and 011710IN with U.S. population) in the Integrated Summary of Safety (ISS).**

    Does the agency agree with this approach?

FDA Response: Yes.

11. **Sponsor is not planning to submit a Risk Evaluation and Mitigation Strategy because the risks of DE-117 are minimal based on data to date and can be adequately managed with routine risk management.**

    Does the agency agree with this approach?

FDA Response: The application should include a discussion of why the proposed drug product risks are minimal based on data to date and can be adequately managed with routine risk management.

Regulatory

12. **Based on the mechanism of action (MOA) of DE-117, its purported risk/benefit profile is believed to be similar to those of other approved prostaglandin analogs. Sponsor does not believe that an Advisory Committee meeting is needed.**

    Can the Agency provide any guidance on this?

FDA Response: A decision regarding the need for an advisory committee meeting will be made after NDA submission.

Clinical Study Report Format

13. **Sponsor has followed the ICH E3 guideline (1995) with respect to the content and general structure (i.e., first level headers) of Clinical Study Reports (CSRs). For the pivotal study CSRs, Sponsor plans to group topics applicable to the study as whole under Section 10, Study Subjects. Specifically, the following three sections will be grouped under Section 10, Study Subjects:**

    - **Demographic and Other Baseline Characteristics (note that in the ICH E3 document, this topic is grouped under Section 11, Efficacy)**
    - **Extent of Exposure (note that in the ICH E3 document, this topic is grouped under Section 12, Safety)**

- **Measurements of Treatment Compliance (note that in the ICH E3 document, this topic is grouped under Section 11, Efficacy)**

The introduction to the ICH E3 guideline (1995) indicates that flexibility in the sequencing and grouping of topics is allowed; this was reiterated in a subsequent questions and answers document ICH issued in 2012 (ICH E3 Implementation Working Group, ICH E3 Guideline: Structure and Content of Clinical Study Reports, Questions & Answers [R1], 06Jul2012). Each CSR will address all the topics in ICH E3 that are relevant for the given study.

Is the above-proposed grouping of sections in CSRs acceptable to FDA?

FDA Response: Yes.

Pediatric Study Plan

14. **Does the agency agree that Sponsor can request a full waiver of pediatric studies for this application?**

FDA Response: Yes, but you should include your explanation within Module 1 for your request for a full waiver of pediatric studies for this application.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

If, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at FDA.gov.[1]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

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.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[5] 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[6] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards

[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[5] https://www.fda.gov/media/88173/download
[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[7] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[8] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[9] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[10]

MANUFACTURING FACILITIES

[7] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[8] https://www.fda.gov/media/88173/download
[9] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[10] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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

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

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

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

Corresponding names and titles of onsite contact:

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

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

/s/

LOIS A ALMOZA
07/08/2019 02:54:50 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111518

MEETING MINUTES

Santen Incorporated
Attention: Raul Brena, RAC
Global Regulatory Affairs Manager
6401 Hollis Street
Suite 125
Emeryville, CA 94608

Dear Mr. Brena:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DE-117 ophthalmic solution.

We also refer to the meeting between representatives of your firm and the FDA on October 16, 2017. The purpose of the meeting was to address feedback received from the Agency in 2015 and to obtain agreement with the Agency on the new proposed DE-117 Clinical, Nonclinical, and CMC plans to support the progression to Phase 3 and the subsequent New Drug Application (NDA).

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

If you have any questions, call 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 Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 16, 2017 from 2:00pm – 3:00pm (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	111518
Product Name:	DE-117 ophthalmic solution
Indication:	treatment of ocular hypertension or open-angle glaucoma
Sponsor:	Santen Incorporated
Meeting Chair:	Wiley Chambers, M.D.
Meeting Recorder:	Lois Almoza, M.S.

FDA ATTENDEES

Wiley Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, M.D.	Clinical Team Leader, DTOP
Lucious Lim, 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)
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Aling Dong, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Chunchun Zhang, Ph.D.	Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ)/ Office of New Drug Products (ONDP)
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Abel Eshete, Ph.D.	Statistical Reviewer, OB/DBIV
Lois Almoza, M.S.	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Raul Brena, RAC	Manager, Regulatory Affairs
Laura Tabor, RAC	Project Manager, Global Project Management
Youquin Tian, M.D., Ph.D.	Associate Director, Regulatory Affairs
Noriko Odani Kawabata, Ph.D.	Program Leader, Program Management

Sho Ota, PharmD	Specialist, Global Pharmacovigilance
Almira Chabi, M.D.	Senior Director, Global Biomedical Sciences
Chien-Feng Chan, Ph.D.	Senior Director, Global Data Science
Chun-Jung Chu, Ph.D.	Associate Director, Pharmaceutical Development
Robert P. Keaney, MSPH	Associate Director, Global Clinical Operations
Fenghe Lu, M.D., Ph.D.	Director, Global Biomedical Sciences
Juanmei Liu, Ph.D.	Associate Director, Biostatistics
Hitomi Takanaga, Ph.D.	Manager, Preclinical Development

BACKGROUND

Santen Incorporated (Santen) requested a meeting to obtain agreement with the Agency on the new proposed DE-117 Clinical, Nonclinical, and CMC plan to support the progression to Phase 3 and the subsequent New Drug Application (NDA) in a July 20, 2017, submission to IND 111518. A Meeting Request Granted letter issued on, August 4, 2017. The Meeting Package was received on September 15, 2017, and Preliminary Comments were sent to Santen via e-mail on October 3, 2017. On October 13, 2017, Santen forwarded slides in preparation for the meeting via e-mail. On October 23, 2017, Santen submitted revised slides to the application on file.

DISCUSSION

Following, in **bold font**, are the questions in the September 15, 2017, Meeting Package. The FDA responses to these questions are in *italic* font. Discussions that took place during the October 16, 2017, meeting are in regular font.

Clinical

1. **Does the Agency agree that the phase I and phase II studies in the US and Japan provide sufficient (b) (4) dose selection (b) (4) to proceed to Phase III clinical development program?**

FDA Response: No. As noted in the EOP2 meeting minutes, we have no objection to the selection of the 0.002% dose for the Phase 3 studies. We agree that the Phase 2 studies provide sufficient exploration of the concentration; we do not agree (b) (4)

Meeting Discussion:

(b) (4)

(b) (4)

(b) (4)

The Agency recommended that Santen study BID vs. QD dosing, in at least one arm of one clinical trial, since Santen has no clinical data on BID dosing.

The Agency had no objection to running a separate BID vs. QD study in parallel with the Phase 3 studies. Additionally, there was no objection to a superiority trial design, at 80% power, to detect a 2mmHg IOP difference. The Agency did not accept mean diurnal IOP as the primary endpoint and recommended the primary endpoint of the mean IOP at each time point for the time points evaluated.

The Agency recommended that Santen extend the treatment phase of the study from four weeks to six weeks due to concern that a four week washout period may not be long enough to eliminate a carry-over effect. Despite the extension of the trial duration to six weeks, the Agency recommended that Santen keep the same number of visits during the treatment phase or cut down to two post-baseline visits.

The Agency suggested that either a Week 1 or Week 2 visit is needed but both are not required. Therefore, instead of 9 time points at post-baseline visits, there could be 6 time-points.

Santen asked since the proposed BID vs. QD trial was not a pivotal trial and BID dosing was not intended for inclusion in the label, would the primary endpoint of a mean diurnal IOP not then be acceptable? Santen stated that if the primary endpoint is the mean IOP at each time point, their understanding is that there would be no need for a multiplicity adjustment.

Regarding mean diurnal IOP, the Agency discussed with Santen that they may miss the opportunity to discover maximum IOP-lowering at particular time point if they do not look at each individual time point. The Agency concurred that there was no need for a multiplicity adjustment for this BID study.

2. **Does the Agency agree that the two phase III studies (one US phase III and one Asian phase III) described in question 2a and 2b will support the submission of an NDA for the proposed indication of reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension?**

FDA Response: The two phase 3 studies (one US phase 3 and one Asian phase 3) would support the filing of an NDA for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. We recommend that at least one of the clinical trials include a bid dosing regimen.

Meeting Discussion: None

a. Does the Agency agree with the proposed US Phase III study design in terms of the primary endpoint, proposed dose selection, masking, control and treatment duration?

FDA Response: To establish noninferiority, the two sided, 95% confidence interval should be within 1.5 mmHg for all IOP measurement time points and within 1.0 mmHg for the majority of IOP measurement time points.

Meeting Discussion: None

b. Does the Agency agree with the Asian phase III study design in terms of the endpoints, proposed dose selection, masking, control and treatment duration?

FDA Response: To establish noninferiority, the two sided, 95% confidence interval should be within 1.5 mmHg for all 9 IOP measurement time points(9, 13 and 17 hrs on Week 1, Week 6 and Month3) and within 1.0 mmHg for the majority of IOP measurement time points.

We recommend that you submit a separate statistical analysis plan for the United States for your proposed Asian phase 3 study. The Agency would plan on analyzing the two trials (US and Asian) in the same manner.

Meeting Discussion: None

c. Does the Agency agree that an additional phase III study can be conducted and would be acceptable as one of the phase III studies for the purposes of the US NDA submission?

FDA Response: We have no objection to an additional phase 3 study; we would expect the NDA to contain complete information from any phase 3 trial which has been completed at the time of NDA submission. We expect the patient database submitted in support of any NDA to be representative of the United States population that might be expected to use the drug product (i.e., patients should have a mixture of iris pigmentation colors).

Meeting Discussion:

Regarding the US phase 3

study (011709IN, TULIP) Santen clarified they will enroll subjects with a mix of iris pigmentation colors.

Additional Comments for 2(a) and (b):

We agree with the proposed primary endpoint and study duration. The protocol synopses however, do not provide sufficient detail regarding the statistical methods for the primary efficacy endpoint in either study. We need to review the full protocols and/or the statistical analyses plans to provide comments on the adequacy of the proposed method. Please consider the comments below when you prepare the full protocol and/or statistical analysis plan:

1. *Please provide a detail account of your proposed mixed model for repeated measures (MMRM) model including the mathematical form of the model. Please also include a mock dataset and a sample SAS code you plan to use to fit the model for our review. We recommend that you use an unstructured covariance matrix and pre-specify a simpler structure in case of convergence issues. We also recommend that you include time as a categorical variable in your model.*

Meeting Discussion:

Santen will provide detailed information on the proposed MMRM model including mathematical form in the statistical analysis plan (SAP) to be submitted in the future. A mock dataset and a sample SAS code used to fit the model will also be included. Santen agrees with the recommendations for the mixed model.

2. *The proposed MMRM method relies on the missing at random (MAR) assumption, a failure of this assumption could lead to a potentially biased result. Please provide the rational for your proposed method and also conduct sensitivity analyses under different assumptions to evaluate the robustness of your results.*

Meeting Discussion:

Santen will have measures in place to minimize the occurrence of missing data. The MMRM method assuming data MAR is deemed appropriate for the primary analysis. Santen will also conduct sensitivity analyses for possible missing not-at-random scenarios to confirm the robustness of the results. Further details will be provided in the SAP.

3. *A higher rate of study discontinuation could hinder the interpretability of the primary efficacy analysis results. For example, the sample size calculation for the ongoing Asian study assumes a 16% study discontinuation rate. Please devise methods to minimize study and/or treatment discontinuations. We strongly recommend that you collect efficacy data on all subjects including those who discontinue the study treatment and those who might receive prohibited or rescue medications.*

Meeting Discussion:

Santen will make efforts to continue to collect data on all subjects including those who discontinue study treatment as well as those who might receive prohibited or rescue medications.

The Agency asked the difference between what is currently being proposed and the BOCF (baseline observation carry forward) in handling missing data. Santen clarified the proposed method was more conservative than the BOCF. For example, in subjects whose IOP is higher during the treatment period than that at the baseline, Santen will use the higher IOP at post-baseline visit to handle the missing data.

3. **Provided that an acceptable benefit-risk profile is confirmed in each phase III study, does the Agency agree that the safety data would be adequate for DE-117 NDA submission?**

FDA Response: The plan appears acceptable provided no unusual safety issues are identified.

Meeting Discussion: None

4. **Does the Agency agree that the corneal endothelial cell count data in these subjects will be sufficient for the submission of the NDA and subsequent approval?**

FDA Response: Approval is a review issue; the Agency had requested corneal endothelial cell count and morphology changes on a minimum of 100 subjects (eyes) in the 0.002% DE-117 group through Month 6. You currently propose to include data on 107 subjects at Month 6.

Meeting Discussion:

Santen asked if the Agency agreed with a plan for 6 months with a minimum of 100 subjects (eyes) and 12 months with approximately 90 subjects (eyes) CECC data from RENGE study without the morphology data. The Agency agrees to Santen's proposal for CECC data submission without inclusion of morphology data.

Nonclinical

5. **Does the Agency agree that the completed nonclinical studies are sufficient for DE-117 to proceed to Phase III?**

FDA Response: We concur with your general approach.

Meeting Discussion: None

a. *Please be aware that the nonclinical studies submitted on September 11 and September 15, 2017 are under review. We will contact you if we have questions regarding these study reports.*

Meeting Discussion: None

b. *You submitted nonclinical reports on September 15, 2017, with the meeting package. Several of the reports have sections not written in English; it is not clear that full English translations were provided. Please identify the location in the IND submission of the English translations for each section, or provide English translations to the IND.*

Meeting Discussion:

Santen will provide the full English translation of the study reports in an amendment to the IND.

6. **Does the Agency agree that the completed nonclinical studies are adequate to support the NDA for DE-117 in the proposed indication?**

FDA Response: We concur with your general approach. Please be aware that additional nonclinical studies may be warranted, if you change the formulation, identify new impurities, or detect unexpected toxicities in the proposed clinical trial(s).

Meeting Discussion:

Santen will conduct additional nonclinical studies if they change the formulation, identify new impurities, or detect unexpected toxicities in the proposed clinical trial(s). The information will be provided in the NDA for DE-117 in the proposed indication.

Chemistry, Manufacturing and Controls (CMC)

7. **Does the Agency agree that the chemical-physical characterization of the two clinical supplies is sufficient to demonstrate the quality equivalence of the two supplies, given that they are prepared at two different facilities and filled in different container closure systems? In addition, does the Agency agree that the difference in the manufacturing site will not disqualify the Asian Phase III study as one of the two pivotal Phase III studies?**

FDA Response: Please clarify which API supplier will be used for the manufacture of the commercial batches. Please clarify which drug substance and drug product manufacturing facilities will be used to manufacture the supplies for each clinical study and for the product that you intend to market. In your NDA submission, all facilities involved in manufacturing the drug substance and drug product should be listed and must be ready for inspection at the time of NDA submission.

If there is a difference between the facilities used in the manufacture of drug supply materials for any of the clinical trials and the drug product intended for marketing in the United States, data comparing of the drug substance quality attributes (including impurities profile and levels), drug product composition, manufacturing process, container closure system and stability data between products manufactured at different facilities should be provided in the NDA submission.

We recommend that you request a CMC-only meeting at the end of phase 2 to discuss any CMC issues.

Meeting Discussion:

Santen clarified that the Drug Substance, manufactured at (b) (4) and the Drug Product, manufactured at (b) (4) will remain the same throughout manufacturing the US Phase 3 clinical supplies, registration stability batches, and commercial product.

The Agency has not identified any additional issues at this time and clarified that the recommendation for a CMC only meeting to discuss CMC matters is suggested to all Sponsors. The Agency request that all listed manufacturing sites be ready for inspection at the time of NDA submission.

Additional Meeting Discussion:

After the planned meeting agenda topics concluded Santen asked an unrelated follow-up question regarding their proposed pediatric plan as discussed in the Meeting Preliminary Comments issued June 9, 2015.

Santen would like the Agency to consider a Pediatric Study Plan waiver for children ages 1-18 years old since they are experiencing enrollment difficulties of pediatric subjects.

Regarding subjects 0 to 1 years of age, the Agency concurs with the difficulties in conducting a study in this population and they have no objection to Santen's submission of a planned waiver request, but this waiver is not likely to be granted until the time of NDA submission when the full application can be reviewed.

Regarding subjects older than 1 to 18 years of age, since Santen has not identified any safety issues that would preclude a study in this patient population, there would not be a basis for a waiver or deferral. The Agency acknowledges the possibility the study may take a long time to enroll subjects and may not be able to fully enroll, but nevertheless, Santen should make the attempt to enroll subjects and the Agency recommends that Santen start enrollment as soon as possible.

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

/s/

WILEY A CHAMBERS
11/15/2017