CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214965Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 70502

MEETING MINUTES

Santen Incorporated
Attention: Kathryn Paunicka, PhD
Sr. Regulatory Affairs Specialist, Global Regulatory Affairs
6401 Hollis Street, Suite 125
Emeryville, California 94608

Dear Dr. Paunicka:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Verkazia (cyclosporine ophthalmic emulsion). We also refer to the meeting between representatives of your firm and the FDA on December 18, 2018. The purpose of the meeting was to discuss the development program of Verkazia (cyclosporine ophthalmic emulsion) and the adequacy of the data for the NDA submission.

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, please call Wendy Streight, PhD, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Date:	December 18, 2018
Time:	12:00 PM – 1:00 PM
Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	70502
Product Name:	Verkazia (cyclosporine ophthalmic emulsion)
Indication:	treatment of (b) (4) vernal keratoconjunctivitis in children from 4 to 18 years of age
Sponsor Name:	Santen Incorporated
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Wendy Streight, PhD

FDA ATTENDEES

Wiley Chambers, MD	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, MD	Clinical Team Leader, DTOP
Rhea Lloyd, MD	Clinical Reviewer, DTOP
Lori Kotch, PhD	Pharmacology/Toxicology Supervisor, DTOP
Aaron Ruhland, PhD	Pharmacology/Toxicology Reviewer, DTOP
Phil Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Abhay Joshi, PhD	Clinical Pharmacology Reviewer, OCP/DCPIV
Chunchun Zhang, PhD	Acting Product Quality Team Leader, Office of Product Quality (OPQ)/New Drug Products Branch III (NDPB-III)
Helen Nagi, PhD	Product Quality Reviewer, Office of Process and Facilities/Division of Microbiology Assessment/Microbiology Branch III
Yan Wang, PhD	Statistical Team Leader, Office of Biometrics (OB)/Division of Biometrics IV (DBIV)

Yunfan Deng, PhD	Statistical Reviewer, OB/DBIV
Erica McNeilly, RPh	Orphan Drug Designation Reviewer, Office of Orphan Products Development, Office of Special Medical Programs
Wendy Streight, PhD	Regulatory Project Manager, DTOP

SPONSOR ATTENDEES

Mourad Amrane, MD	Senior Director Clinical Science, Global Biomedical Science
Franz Buchholzer, PhD	Vice President, Global Regulatory Affairs
Chun-Jung Chu, PhD	Associate Director, Pharmaceutical Development
(b) (4)	(b) (4), Consultant
Dahlia Ismail, MSc	Associate Director Clinical Science, Global Biomedical Science
(b) (4)	(b) (4)
Julie Katz, MPH, MPhil	Pharmacoepidemiologist, Global Pharmacovigilance
Kathryn Paunicka, PhD	Senior Regulatory Affairs Specialist, Global Regulatory Affairs
Usha Srinivasan, MS, RAC	Senior Director, Global Regulatory Affairs
Laura Tabor, MSE, RAC	Project Manager, Global Project Management
Hitomi Takanaga, PhD, RAC	Manager, Preclinical Development

BACKGROUND

Verkazia, is a sterile, preservative-free, (b) (4) Cyclosporine A (CsA) emulsion. Verkazia is being developed by Santen for a (b) (4) vernal keratoconjunctivitis, a rare disorder in children. Orphan Drug designation was granted for Verkazia on May 4, 2007.

The purpose of the meeting was to discuss the development program of Verkazia and the adequacy of the data for the NDA submission. In preparation for this meeting, a briefing package was submitted by Santen on November 15, 2018. Preliminary responses to the questions posed in the briefing package were sent to Santen on December 6, 2018. In response to the Division's preliminary comments, Santen submitted correspondence requesting to focus the meeting discussion on Questions 1 and 8. Prior to the meeting, Santen provided the Division with a slide presentation that summarized the Verkazia data to discuss during the meeting.

DISCUSSION

Following, in **bold**, are the questions submitted in the November 15, 2018, meeting package. The FDA's Preliminary Responses to these questions are in *italics*, and the Meeting Discussion for Questions 1 and 8 are in normal font.

CLINICAL

1. **Santen believes that the pivotal trial, VEKTIS, together with data from the supportive dose finding study, NOVATIVE, support the efficacy and safety of Verkazia in children with VKC. In the context of both a pediatric and an orphan condition, does the Division concur that the, double-masked, vehicle-controlled trial VEKTIS along with data from NOVATIVE, as outlined in the briefing document are sufficient to support the NDA filing, review, and potential approval consideration of Verkazia? Does the Agency agree that the safety profile of children support the benefit risk?**

   FDA Response: *Disagree. The data from NOVATIVE and VEKTIS are unlikely to be sufficient to support the approval of an NDA. Safety and efficacy are recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials. At least two replicated trials are recommended to demonstrate robustness of results for the indication.*

   The primary efficacy endpoint in the NOVATIVE was not statistically significant. The clinical significance of the primary endpoint for the VEKTIS studies is not known.For an indication of vernal keratoconjunctivitis we recommend that the primary endpoint be a subjective evaluation of ocular itching/comfort by the patient and an objective evaluation of conjunctival papillae by the examining physician. Statistically significant improvement in ocular itching/discomfort and complete elimination of conjunctival papillae are recommended as clinically significant.

   A complete NDA review is required to assess the benefit risk of the safety profile in children.

   Meeting Discussion: The Division reiterated its recommendation that safety and efficacy be demonstrated in at least two adequate and well-controlled trials. It was recommended that these studies include endpoints that evaluated changes in papillae, keratitis and itching. Improvement in the endpoints of papillae (or keratitis) and itching would be in alignment with the Division's previous recommendations.

   The Division stated that it was not in agreement with the assigning penalties to the CFS score because the applied penalties for rescue medication use were arbitary. The effect of rescue medication, depending on the medication and the timing may have affected the score significantly more or less than the penalty assigned. The Division recommended that Santen consider removing all patients who had to use rescue medication. The Division suggested that Santen consider reanalyzing the VEKTIS study using non-penalized scores of keratitis as a sign and itching as a symptom without averaging the scores over several months. Santen remarked that the EMA requested that the data be analyzed using the average of the 4 months of treatment. The Division disagreed suggesting that a better approach would be to determine the onset of action and the duration of effect of the product.

Santen detailed their rationale for believing that Verkazia should qualify for fast track designation, breakthrough therapy and a priority review. The Division noted that there were already two drug products approved for this indication and that Santen's product had not demonstrated superiority to either.

Santen suggested that the VEKTIS study was sufficiently robust as to potentially be equivalent to two studies. The Division agreed to review additional analyses of the VEKTIS study including proposals to demonstrate the robustness of the results by spliting the study into multiple studies. The adequacy of the results would be a review issue. Alternatively, the Division recommended that Santen conduct an additional adequate and well controlled clinical trial.

2. **Santen proposes to submit the integrated safety data from VEKTIS and NOVATIVE in the Integrated Summary of Safety Section of the Verkazia NDA. Does the Agency agree? Are there any specific data depictions which the Division will require for NDA review of safety issues? How will the Division identify adverse events of special interest?**

   FDA Response: *Your proposal for submission of the integrated safety data for all clinical studies conducted with Verkazia in the Integrated Summary of Safety will be acceptable at the time of NDA filing. Presentation of adverse events by treatment group, demographic factors, previous and concomitant medications, etc. would be informative.*

NONCLINICAL

3. **Santen has performed a nonclinical program to support the planned NDA. Santen believes that the completed nonclinical program and publicly available information on cyclosporine are adequate to support the NDA for the use of Verkazia to treat VKC. Does the Agency agree that the nonclinical package is sufficient to support the review of the NDA? What literature review or products of reference would FDA require as the basis for a complete nonclinical package?**

   FDA Response: *Presuming all recommended nonclinical elements (e.g. pharmacology, pharmacokinetics, chronic ocular toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.) are provided/addressed in a 505(b)(1) or 505(b)(2) application (i.e., via conduct of original studies or by reliance); and data that you do not own are adequately bridged, additional nonclinical data will not be needed. The adequacy of data to support your application will be a review issue.*

General Nonclinical Advice for 505b2 NDAs:

All recommended nonclinical elements should be provided to the NDA, either directly (studies conducted by you, or data for which you have right of reference) or by reliance on literature or FDA's findings of safety and effectiveness for a listed drug(s). Reliance on data that you do not own or have right of reference to will require an adequate

bridging strategy (e.g. comparative systemic PK, comparative dose). A detailed description regarding how you intend to bridge data that you don't own, or have right of reference to, should be provided in the NDA.

1. *If literature is being relied upon to support the NDA, published literature relevant to your product should be considered, and relevant data should be summarized in the NDA.*
   a. *Include a summary of all published nonclinical literature being relied upon and a copy of all publications cited.*
   b. *The nonclinical summary is typically organized to address each of the nonclinical elements (e.g. pharmacology, pharmacokinetics, local toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.).*
   c. *A copy of each cited article should be provided. Please note that review articles cannot be relied upon to support an application; the source articles which contain full study data should be provided or incorporated by reference.*
   d. *Published data is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. In your integrated summary, provide discussion of the potential impact of study shortcomings (e.g. insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.*
   e. *Please identify any listed drug(s) described in the published literature (e.g., trade name(s)). Reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s).*
   f. *You will need to be able to bridge (e.g. via comparative dose or PK) any published safety data that you plan to rely on to fulfill nonclinical requirements. We advise that you provide information in the NDA discussing how you intend to bridge data contained in each of the published studies you plan to rely on. A discussion regarding the impact of formulation differences between your product and those used in published studies would also be helpful. The adequacy of the published data to support your 505b2 NDA application will be a review issue.*

2. *Please note that non-US labeling or non-US regulatory authority assessments may not be relied upon as they are neither FDA's findings related to a listed drug, nor are they published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature.*

3. *FDA discipline reviews cannot be relied upon to support an 505(b)(2) NDA application. FDA finding of safety and efficacy is captured in the product labeling, and may include findings that can be inferred from fact of approval. If you intend to rely on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate. You should establish a "bridge" (e.g., via comparative pharmacokinetic data) between your proposed formulation, and the listed drug using the approved dose/route. Ensure study*

measurements include a timepoint at peak exposure (Tmax) following each administration. If exposure levels following ocular topical administration of your proposed formulation (at intended clinical dose) are less than or equal to that of the listed drug (at approved dose/route), then reliance upon the listed drug would be considered scientifically justified. If exposure levels using your formulation exceed those of the listed drug, then additional toxicity studies may be needed to support the increased exposure.

4. *The regulatory requirements for a 505(b)(2) application, including an appropriate patent certification or statement, apply to each listed drug upon which you rely.*

5. *Impurity specifications that exceed qualification limits specified in the ICHQ3 guidances should be adequately qualified and safety data supporting conditions of use should be provided in the NDA submission. Ensure that both systemic and local toxicity are addressed.*

6. *Formulation excipients should be adequately qualified and safety data supporting conditions of use should be provided in the NDA submission. Ensure that both systemic and local toxicity are addressed.*

7. *For the NDA, labeling should comply with the Pregnancy and Lactation Labeling Rule (PLLR). For more information, please see the final rule.*

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm

PHARMACEUTICAL QUALITY

4. Does the Agency agree that the CMC information outline provided in Section 5 is adequate for an NDA submission? Santen will provide the details of the CMC development and the associated reports in the NDA submission.

FDA Response: The CMC information outline seems reasonable. The final determination of acceptability will be determined during the review of the NDA.

You are reminded to refer to the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Final 11/1994.

Sterilization validation information that should be submitted in the NDA application includes (and is not limited to) the following:

- *Validation of the sterilization process for the bulk product and equipment.*
- (b) (4) *process/ media fill simulation that includes simulation of proposed holding time.*
- *A description of the environmental monitoring program.*

- *Container closure integrity studies for the container closure system that will be used in commercial production.*
- *Method suitability study for the sterility test.*

DATA MANAGEMENT

5. **Santen is planning to submit Case Report Forms (CRFs) for subjects that experience a serious adverse event, an event of special interest, discontinued the study before completion, or died while on the VEKTIS study. Does the Agency agree with the proposed plan for the CRFs in the NDA submission? Are any additional analyses required for safety or efficacy review?**

   FDA Response: Acceptable.

6. **Santen proposes to provide the datasets in the SAS format. Does the Agency agree with the proposed plan for the electronic dataset submission in the NDA?**

   FDA Response: Your proposal appears acceptable. In addition, please submit all the SAS program codes used to produce the efficacy and safety analysis results presented in the study reports of the both studies (NOVATIVE and VEKTIS). Please also provide define documents to explain the purpose of the submitted SAS codes.

REGULATORY

7. **Does the Agency agree that the clinical development plan and the totality of evidence for the safety and efficacy of Verkazia are sufficient for NDA review and approval for the indication "treatment of (b) (4) vernal keratoconjunctivitis in children from 4 through 18 years of age"? If not, can the agency clarify any issues or concerns regarding the proposed language?**

   FDA Response: Disagree. Refer to the response to Question 1.

8. **Santen believes that Verkazia fulfills the requirements for Fast Track and/or Breakthrough Designation and qualifies for a priority review. Does the agency agree?**

   FDA Response: Disagree. Your program has not demonstrated that your proposed product is superior to other products approved for your proposed indication (i.e., cromolyn sodium ophthalmic solution).

   Meeting Discussion: Santen reiterated their argument that Verkazia should meet the requirement for Priority Review, clarifying that their pivotal study demonstrated clinical and statistically significant results in the signs, symptoms and quality of life of children with VKC. The Division noted that the guidance on priority reviews included the expectation that a product demonstrate superiority or an advantage over the currently available therapies in order to be granted priority review. Presently, there are two

products approved for VKC and Santen's product has not demonstrated superiority to either product. Therefore, in order to be granted Priority Review, Santen would have to submit data showing that Verkazia is superior to the currently approved products.

9. **Santen plans to file the NDA under the 505(b)(2) pathway. Does the Agency agree with the route, and with the use of CsA as the reference listed drug (RLD)?**

   FDA Response: *We have no objection to the filing of your application as a 505(b)(2), although it is not clear what information is needed in your application that you do not have a right to reference. You should use the specific reference listed drug (RLD) corresponding to the data that you utilize that you do not own or have right of reference.*

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.

PRESCRIBING INFORMATION

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

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

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 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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.

ATTACHMENTS AND HANDOUTS

The slide presentation submitted via email on December 17, 2018, is attached.

25 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.

/s/

WILEY A CHAMBERS
12/25/2018 10:19:43 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 70502

MEETING MINUTES

Santen, Inc.
Attention: Adaku Iwueze-Uwahemu
Senior Regulatory Affairs Specialist
2100 Powell Street, 16th Floor
Emeryville, CA 94608

Dear Ms. Iwueze-Uwahemu:

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

We also refer to the meeting between representatives of your firm and the FDA on December 7, 2015. The purpose of the meeting was to discuss additional clinical information to support (b) (4) for the treatment of (b) (4)

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 Christina Marshall, Regulatory Project Manager at (301) 796-3099.

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
Sponsor's presentation

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Pre-NDA

Meeting Date and Time: December 7, 2015
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 70502
Product Name: (b) (4) (cyclosporine ophthalmic emulsion)
Indication: (b) (4)
Sponsor/Applicant Name: Santen Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Christina Marshall

FDA ATTENDEES
Renata Albrecht, Director, Division of Transplant and Ophthalmology Products, (DTOP)
Wiley A. Chambers, Deputy Director, DTOP
William M. Boyd, Clinical Team Leader, DTOP
Rhea Lloyd, Clinical Reviewer, DTOP
Yan Wang, Biometrics Team Leader, Division of Biometrics IV (DBIV)
Yunfan Deng, Biometrics Reviewer, DBIV (on the phone)
Christina Marshall, Regulatory Health Project Manager, DTOP

SANTEN ATTENDEES
Mourad Amrane, Director, Global Clinical Science
Franz Buchholzer, Vice President, Global Regulatory Affairs
Jinzhong Zhang, Associate Director, Preclinical Development
Michael Woods, Associate Director, Regulatory Affairs
Dahlia Ismail, Senior Manager, Global Clinical Science
Lening Zhang, Senior Biostatistician II, Global Data Science
Denise Lai, Senior Manager, Project Management
(b) (4)

BACKGROUND

The Sponsor is developing [redacted] for the treatment of [redacted]. The objective of this pre-NDA meeting was to discuss additional data in order to support of an NDA application for [redacted]

The Sponsor submitted a briefing document on November 6, 2015. Preliminary responses to the questions posted in the briefing document were sent to the Sponsor on December 1, 2015. Based on these comments, the sponsor indicated that they would like to focus the discussion on the question 1, and forwarded via e-mail a presentation (attached to these minutes) to be the basis for discussion.

For the purposes of these minutes, the questions posted by the Sponsor in the briefing documents are in **bold** format, the preliminary responses are in *italics* and the meeting discussions are in normal font.

DISCUSSION

Does the FDA agree that the additional supporting clinical information from Santen and the literature provided in this briefing document supports the approval of [redacted] for the treatment of [redacted]?

[redacted]

(b) (4)

[redacted]

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
The Division will issue the minutes within 30 days.

ATTACHMENTS AND HANDOUTS
None

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/s/

WILEY A CHAMBERS
12/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 70502

MEETING MINUTES

Santen, Inc.
Attention: Adaku Iwueze-Uwahemu
Senior Regulatory Affairs Specialist
2100 Powell Street, 16th Floor
Emeryville, CA 94608

Dear Dr. Iwueze-Uwahemu:

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

We also refer to the meeting between representatives of your firm and the FDA on July 22, 2015. The purpose of the meeting was to discuss and reach agreement on the CMC, non-clinical and clinical plans to support the filing of an NDA submission.

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 Judit Milstein, Chief, Project Management Staff, at (301) 796-0763.

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
Sponsor's presentation

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	pre-NDA
Meeting Date and Time:	July 22, 2015, 2:00-3:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 70502
Product Name:	(b) (4) (cyclosporine topical ophthalmic emulsion)
Indication:	(b) (4)
Sponsor:	Santen Inc.
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Judit R. Milstein

FDA ATTENDEES

Wiley A. Chambers, Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William M. Boyd, Clinical Team Leader, DTOP
Rhea Lloyd, Clinical Reviewer, DTOP
Martin Nevitt, Clinical Reviewer, DTOP
Lucious Lim, Clinical Reviewer, DTOP
Aaron Ruhland, Pharmacology/Toxicology Reviewer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Anamitro Banerjee, CMC Lead, Office of Pharmaceutical Quality
Denise Miller, Microbiology Reviewer, Microbiology Assessment Branch II
Yunfan Deng, Biometrics Reviewer, Division of Biometrics IV (DBIV)
Yan Wang, Biometrics Team Leader, DBIV
Yongheng Zhang, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCPIV)
Philip Colangelo, Clinical Pharmacology Team Leader, DCPIV (on the phone)
Judit Milstein, Chief, Project Management Staff, DTOP
Shrikant (Suresh) Pagay, CMC Reviewer, OPQ (on the Phone)

SANTEN ATTENDEES

Mourad Amrane, Medical Affairs Director
Franz Buchholzer, VP, Global Regulatory Affairs

Jinzhong Zhang, Associate Director, Preclinical Development
Michael Woods, Associate Director, Regulatory Affairs
Dahlia Ismail, Senior Manager, Medical Affairs
Lening Zhang, Sr. Biostatistician
Mohamed Ibrahiem, Sr. Manager, Global Regulatory Affairs
(b) (4), Consultant

BACKGROUND

The Sponsor is developing (b) (4) for the treatment of (b) (4) The objective of this pre-NDA meeting was to discuss and obtain agreement on the proposed CMC, non-clinical and clinical dossier in support of an NDA application for (b) (4).

The sponsor submitted a briefing document on June 22, 2015. Preliminary responses to the questions posted in the briefing document were sent to the sponsor on July 17, 2015. Based on these comments, the sponsor indicated that they would like to focus the discussion on the Clinical Comment 1, and forwarded via e-mail a presentation (attached to these minutes) to be the basis for discussion.

DISCUSSION

For the purposes of these minutes, the questions posted by the sponsor in their briefing document are in **bold** format, the preliminary responses are in *italics* and the meeting discussions are in normal font.

Chemistry, Manufacturing and Controls

Question 1
Does the Agency agree that the CMC package for (b) (4) is generally adequate to support the planned NDA?

FDA Comments:
Drug Substance: We do not agree that Certificate of Suitability (CEP) for cyclosporine is adequate information for NDA. Please provide a complete package for the drug substance (description, physical chemical properties, fermentation/synthesis, information on starting material, manufacturing facilities, test methods, methods validation, specifications, batch analysis data, container closure, stability protocol/data, retest period, etc.). Alternatively you can provide reference to a DMF.

Drug product: Information provided in the briefing document includes the manufacturing facilities, manufacturing process, specifications, and stability studies. The NDA should also address pharmaceutical development, physical stability of emulsion, container closure, leachable /extractable, test methods, validation etc.

The Stability studies should include a minimum of 12 months data on 3 primary batches. Include impurities (degradation products) as per the ICH format (specified impurities etc.). Include particulate matter in the specifications and monitor through the shelf life per USP test for ophthalmic drug products.

The proposed mean droplet size (b) (4) *nm is very wide. This should be tightened and an upper size limit should be included in addition to the mean droplet size in the specifications.*

We recommend that you request a CMC only meeting if you have any questions or concerns in the CMC section.

Meeting Discussion:
The Sponsor stated that they will be providing a DMF for the drug substance, and that for the drug product, they will provide the information as requested by the Agency.

Sterility: The information provided for the in process and release specifications appear adequate from a quality microbiology perspective. Final determination of acceptability will be determined during the review of the NDA.

We refer you to the Guidance for Industry "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" Final 11/1994, for further information.

Sterilization validation information that should be submitted in the NDA application includes (and is not limited to) the following:

- *Validations of the sterilization process for the bulk product and equipment*
- *Media fill simulations that include simulation of holding times*
- *Environmental monitoring program*
- *Container-closure integrity studies for the container-closure system that will be used in commercial production*
- *Method suitability study for the sterility test*

Meeting Discussion:
The Sponsor stated that they had no additional comments regarding the sterility recommendations.

Nonclinical

Question 1
Santen previously described the non-clinical testing conducted with (b) (4)**, and the Agency found this testing to be adequate to support a future NDA (EOP2 Meeting, July 2006, Pre- NDA Meeting April 2010). Does FDA continue to agree that the completed non-clinical studies with** (b) (4) **are adequate to support the planned NDA?**

FDA Comments:
Presuming that you can adequately bridge the data that you are relying upon (e.g., listed drug, published data), then the submitted nonclinical studies may be sufficient to support your NDA. In your NDA, include a summary of all published nonclinical literature being relied upon, and a copy of each publication cited. SBAs and FDA discipline reviews are considered summary data and cannot be relied upon to support an NDA. The adequacy of the bridge and the data you are relying upon to support your NDA will be a review issue.

In the NDA submission, please provide a side-by-side comparison of all formulations used in the nonclinical studies and the clinical formulation. Provide adequate safety data (i.e., qualification data) for any impurity that exceeds qualification limits, as specified in the ICHQ3 guidances. Ensure that all excipients are qualified for ocular use. For further reference:

Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079250.pdf

Meeting Discussion:
The Sponsor stated that they will provide in the NDA submission adequate safety data and side-by-side comparison of all formulations used in the non-clinical and clinical studies.

Clinical

Question 1
Does the Agency agree that the completed clinical trials for (b) (4) **are adequate to support an NDA for the proposed indication of** (b) (4)

(b) (4)

FDA Comments:
Disagree. (b) (4)

(b) (4)

(b) (4)

Question 2
Santen plans to provide case report forms (CRFs) from 2 Phase 3 studies for all subjects. Does the Agency agree with Santen's proposal for only including CRFs from phase 3 studies?
FDA Comments:
Case report forms should be provided for all patients in all studies who did not complete the study for any reason.

Meeting Discussion:
The Sponsor stated that they will provide CRFs for all patients, for all patients who did not complete the studies, for any reason.

Regulatory
Question 1
Santen proposes a waiver of pediatric studies as required by the Pediatric Research Equity Act (PREA) for (b) (4) because studies are highly impracticable for children and adolescents < 18 years of age, because the disease is rare in this age group. The Initial Pediatric Study Plan was submitted to the Agency on May 26, 2015. Does the agency agree with the proposed pediatric plan?

FDA Comments:
The Division agrees with your plan to submit a request for a waiver of pediatric studies required by the Pediatric Research Equity Act (PREA) at the time of NDA submission.

Meeting Discussion:
The Sponsor stated that they will include in their NDA a request for a waiver of pediatric studies.

Biometrics
Question 1
The current datasets for all studies to be included in the proposed NDA are not CDISC compliant. For each study, the data was not collected in a CDISC format for either studies collected via paper or electronically. There was also no subsequent mapping done to format the data into the SDTM or ADaM structures and therefore the study reporting were created from clinical and analytic datasets in structures that benefited the reporting

of the study, rather than in compliance with CDISC guidelines. Is it acceptable for Santen to include the datasets as is? If not, would it be acceptable to include only SDTM datasets for the studies?

FDA Comments
We recommend you submit both SDTM datasets and the existing datasets you currently have. In addition, please submit all SAS program codes for generating the efficacy and safety results in your study report.

Meeting Discussion:
The Sponsor stated that they will provide SDTM and original datasets as well as SAS program codes as requested by the Division.

Additional FDA Comments:

We recommend that you attempt to assess the systemic exposure to cyclosporine with the to-be-marketed formulation and at the final clinical dosage regimen during the clinical development program for (b) (4)

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
The Division will issue the minutes within 30 days.

ATTACHMENTS
Slide presentation provided by the sponsor

505(b)(2) applications:
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, in part, 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, in part, 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., trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
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.

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/s/

WILEY A CHAMBERS
08/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 70502

MEETING MINUTES

Novagali Pharma S.A.
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Dear (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cyclosporine Topical Ophthalmic Emulsion (NOVA 22007).

We also refer to the meeting between representatives of your firm and the FDA on April 7, 2010. The purpose of the meeting was to discuss results of the clinical trials conducted in support of a NDA for the drug product.

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

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301)796-0797.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 7, 2010, 3:00 – 4:00 PM
Meeting Location: 10903 New Hampshire Avenue, Building 22, Room 1419, Silver Spring, MD 20993

Application Number: IND 70502
Product Name: NOVA22007 - Cyclosporine Topical Ophthalmic Emulsion
Indication: Keratoconjunctivitis (b) (4)
Sponsor/Applicant Name: Novagali Pharma S.A.

Meeting Chair: Wiley Chambers, M.D.
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective and Ophthalmology Products
Wiley Chambers, MD, Acting Director
Conrad Chen, PhD, Pharmacology and Toxicology Reviewer
Yunfan Deng, PhD, Statistical Reviewer
Lucious Lim, MD, Medical Officer
Rhea Lloyd, MD, Medical Officer
Denise Miller, PhD, Microbiology Reviewer
Martin Nevitt, MD, Medical Officer
Linda Ng, PhD, Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment
Alison Rodgers, Project Manager
Wendy Schmidt, PhD, Pharmacology and Toxicology Team Leader
Mark Seggel, PhD, Chemistry Reviewer
YanWang, PhD, Statistical Team Leader

SPONSOR ATTENDEES

Novagali Pharma S.A. (Novagali)
Mourad Amrane, MD, Director Medical Affairs
(b) (4), DVM, Advisor to Novagali
Mohamed Ibrahiem, Regulatory Affairs Pharmacist
(b) (4), MD, Consultant
(b) (4), MD, Advisor to Novagali
Jean-Sebastien Garrigue, Director Pharmaceutical Research and Development

BACKGROUND

Novagali submitted a request for a Pre-NDA Meeting on January 14, 2010, to discuss results of the clinical trials conducted in support of a NDA. A briefing package was submitted on

March 5, 2010. The Division provided Novagali with responses to the questions outlined in the briefing package via email on April 6, 2010. The meeting served to clarify the Division's responses.

In response to questions in the March 5, 2010 background package, the following responses were given. The format provides the firm's questions in plain lettering followed by the Division's responses in italics. The discussion points from the meeting are provided below.

CMC

1. **Does the Agency agree that the CMC package for (b) (4), as described in this briefing document, is generally adequate to support the planned NDA?**

Division Response:
It appears that two (2) drug product formulations, containing either (b) (4) or CKC, are proposed for commercialization. Please indicate which formulation you intend to commercialize under the forthcoming NDA.

Determine the average droplet size of product delivered from the (b) (4) vials (not to be confused with the mean (b) (4) droplet size).

The lower limits for product pH both at release and on stability should be justified with batch and stability data.

For tests where both USP and Ph.Eur. monographs are available, the USP method should be used unless adequate justification is provided.

Determine the stability, including (b) (4), of the drug product removed from the foil pouch. This can be done as a one time study on one batch. The period covered should include the period of use of the contents of one pouch (days) through at least twelve (12) months.

Provide primary stability data from three batches of the drug product with the commercial formulation.

The impurities/degradation products should be listed in the drug product specification as follows:

Each specified identified leachable in ppm
Each specified unidentified leachable in ppm
Total leachables in ppm

Each specified identified degradation product in %
Each specified unidentified degradation product in %
Any individual unspecified impurity (including any peaks observed that are not listed above) in %
Total impurities

Justify the acceptance criterion of NMT [redacted]% for individual unspecified impurity in the drug product.

Provide a Letter of Authorization for the Drug Master File covering the LDPE [redacted] used in the manufacture of the [redacted] vials.

Perform a leachable/extractables study on the [redacted] vial. A one time study of one batch on stability through the proposed expiry is acceptable.

Provide Letters of Authorization for all Drug Master Files cited in the NDA.

Provide a list of all manufacturing and testing facilities, along with contact information, and confirm that all facilities are ready for inspection.

Explain the notation "[redacted], [redacted] Explain this discrepancy.

Generally, the CMC package is adequate to support the planned NDA from a quality microbiology perspective. Please refer to the 1994 Guidance for Industry for the Submission of Documentation for Sterilization Process validation in Applications for Human and Veterinary Drug Products and the CDER MaPP 5040.0 Product Quality Microbiology Information in the Common Technical Document for further guidance.

We recommend that endotoxin testing should be performed as a release test supported by method suitability (enhancement/inhibition) studies. A target endotoxin acceptance criterion of ≤ [redacted] EU/mL should be considered.

NON-CLINICAL DEVELOPMENT

2. Novagali previously described the non-clinical testing conducted with [redacted], and the Agency found this testing to be adequate to support a future NDA (EOP2 Meeting, July 2006). Does FDA continue to agree that the completed non-clinical studies with [redacted] as described in the pre-meeting briefing package, are adequate to support the planned NDA?

Division Response:
Yes, the submitted non-clinical studies are adequate to support the NDA.

CLINICAL DEVELOPMENT

3. Does the Agency agree that the completed clinical trials for (b) (4) as described in this briefing document, are adequate to support an NDA for an indication of treatment of (b) (4)?

Division Response:

(b) (4)

4. If an additional trial is required, is the proposed study design provided in the pre-meeting briefing package adequate to support an NDA, when combined with the completed clinical trials?

Division Response:

(b) (4)

Does the Agency agree with the patient population definition and, the primary endpoint taken into account targeted indications?

Division Response:

(b) (4)

DISCUSSION

Novagali presented slides to serve as background for the discussion (attached).

- Regarding clinical trial requirements for an NDA for a (b) (4)

(b) (4)

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- Novagali will develop and submit a proposal for another study.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
- Novagali will provide their statistical analysis plan for Study (b) (4) for the Division's review.
- Novagali will submit the full study report for Study (b) (4) along with a request for feedback to the IND.
- The Division will review the article by (b) (4) that appeared in the (b) (4) issue of The Archives of Ophthalmology.
- Novagali will develop and submit a proposal for another study.
- FDA will provide Novagali with meeting minutes within 30 days.

ATTACHMENTS AND HANDOUTS
- Division's Responses to Meeting Package Questions
- Novagali's slides

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-70502	GI-1	NOVAGALI PHARMA SA	NOVA22007

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/s/

WILEY A CHAMBERS
04/21/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 70,502

Novagali Pharma SA
(b) (4)

Dear (b) (4):

Please refer to your Pre-Investigational New Drug Application (PIND) file for NOVA22007 Cyclosporine Topical Ophthalmic (b) (4).

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2006. The purpose of the meeting was to discuss the Phase 3 clinical trials for NOVA 22007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

MEETING DATE: July 19, 2006
TIME: 11:00 AM
LOCATION: 10903 New Hampshire Avenue, Silver Spring, MD 20903
APPLICATION: 70,502
DRUG NAME: NOVA 22007
TYPE OF MEETING: End-of-Phase 2

MEETING CHAIR: Wiley Chambers, M.D.

MEETING RECORDER: Alison Rodgers

FDA ATTENDEES:
Division of Anti-Infective and Ophthalmology Products
Wiley Chambers, MD, Deputy Director
Lillian Gavrilovich, MD, Deputy Director
William Boyd, MD, Clinical Team Leader
Linda Ng, PhD, Chemistry Team Leader
Martin Nevitt, MD, Medical Officer
Rhea Lloyd, MD, Medical Officer
Jennifer Harris, MD, Medical Officer
Amy Nostrandt, PhD, Pharmacology Team Leader (Acting)
Conrad Chen, PhD, Pharmacologist
Kimberly Bergman, PhD, Clinical Pharmacologist
Thamban Valappil, PhD, Statistical Team Leader
Yunfan Deng, PhD, Statistician
Alison Rodgers, Project Manager

EXTERNAL CONSTITUENT ATTENDEES:
Novagali Pharma SA
Florinch Binlich, MD, Head,Clinical Development/Regulatory Affairs
(b) (4), Regulatory Consultant
Gregory Lambert, PhD, Vice President, Rx Pharmaceutical Development
(b) (4), Consultant
Jerome Martinez, MD, CEO

BACKGROUND: On May 22, 2006, Novagali Pharma SA (Novagali) requested a meeting to discuss the Phase 3 clinical trials for NOVA 22007. The meeting was granted and scheduled for July 19, 2006. On June 15, 2006, Novagali submitted a meeting package. The Division's draft responses to the questions outlined in the meeting package were sent to Novagali via facsimile on July 12, 2006.

GENERAL COMMENTS: The questions from the background package are restated below in bold. Each question is then followed by FDA comments in italics. These are identical to the comments provided to Novagali on July 12, 2006. The comments are followed by bulleted meeting discussion points.

Novagali provided slides as background information for discussion at the meeting. (Note: The slides will be submitted to the PIND.)

MEETING OBJECTIVES: Novagali wished to obtain clarification of the Division's responses to the questions submitted on June 15, 2006, with the NOVA 22007 pre-IND briefing document.

DISCUSSION POINTS:

PRECLINICAL TESTING REQUIREMENTS

1. **Is the proposed preclinical development package adequate for an IND submission?**

FDA Comment: *The information appears to be adequate to support the proposed trial.*

No Meeting Comments

2. **Is the proposed preclinical development package adequate for an NDA submission?**

FDA Comment: *Yes, assuming there are no additional review issues.*

No Meeting Comments

3. **If not, what additional testing is required in support of initiation of the proposed Phase 3 trials? In support of an NDA?**

FDA Comment*: There do not appear to be additional tests required at this time.*

No Meeting Comments

CMC REQUIREMENTS

1. **Is the new proposed specification established for the finished drug product acceptable to FDA?**

FDA Comments:

a. *In general, acceptable for the tests; acceptance criteria will be deferred to the NDA. Please clarify what USP* (b) (4) *test is performed. For unknown impurities and degradation products, individual unknown should be specified at NMT* (b) (4).

b. (b) (4) *is included in the specification but missing in the stability report.*

c. *The storage conditions for the* (b) (4) (b) (4)

d. *The specific* (b) ( ) *will need to include controls to ensure uniformity from batch to batch.*

Meeting Comments:

- Novagali noted that there was an error in the release specification data; the rows shifted in error. They inquired about the individual unknown at NMT (b) (4)%. The Division stated that ophthalmic products except for very low strength product will contain an individual

unspecified impurity at NMT (b)(4)%. Unspecified impurities using retention times may be listed. Attempts should be made to identify the impurities.

- Novagali stated that they thought they had applied the appropriate storage conditions of (b)(4) according to ICH Q1A R2. The Division responded that (b)(4)% RH may be more appropriate for (b)(4). Novagali explained that the product will be sealed in an aluminum foil pouch and thus asked if the (b)(4)% RH is acceptable. The Division agreed.
- Novagali presented their data on (b)(4) and inquired if it would be acceptable to achieve (b)(4) (b)(4) (b)(4) Novagali will follow up with supporting information in the IND.

CLINICAL PROTOCOL

1. **Is the study design proposed by Novagali for the clinical trial of NOVA22007 in the treatment of (b)(4) keratoconjunctivitis (b)(4) acceptable to the Agency? If not, what modifications does the FDA suggest to ensure that the study results serve to support an NDA application?**

FDA Comments:

(b)(4)

Meeting Comments:

- Novagali stated that (b)(4) (b)(4) Novagali asked if this information would support the use of (b)(4) as excipients and not actives. The Division responded that it would review this information in the IND.

(b)(4)

(b) (4)

No Meeting Comments

3. **Is the proposed patient's population adequate to support an NDA application in treatment of (b) (4) KCS? If not, what specific recommendations does the Agency have regarding patients' inclusion criteria?**

FDA Comments: *Yes.*

No Meeting Comments

4. **The proposed scale for assessment of corneal fluorescein staining is based on a 'modified' (b) (4)**

(b) (4)

(b) (4) **Is this an acceptable scale? If not, which scale does the FDA suggest to ensure that the study results serve to support an NDA application?**

FDA Comments: *The proposed scale is not acceptable. A* (b) (4)

Meeting Comments:

- (b) (4)

  Novagali asked about the Division's rationale for requiring complete resolution of corneal staining.
- The Division responded that complete resolution of corneal staining demonstrates clinical significance which the Division defines as a decrease in the risk of subsequent infections or ulceration.
- The Division stated that zero corneal staining does not have to be achieved if a subjective and objective endpoint are both evaluated. A twenty-five percent change as the proposed scale would be acceptable. Novagali expressed its concern that this standard on this scale is unrealistic for clinical trials. The Division responded that a 4-point scale does not have to be used; an 8-point scale is acceptable.

5. **Is the proposed primary efficacy endpoint** (b) (4)

(b) (4)

FDA Comments:

a. *No.* (b) (4)

b. *The proposed scale is not acceptable.* (b) (4)

No Meeting Comments

6. **We propose that the study patients assess the intensity and frequency of symptoms of ocular discomfort (unrelated to instillation of the study medication) by means of a visual analog scale. Will FDA accept this approach? What recommendations does the Agency have regarding appropriate visual analog scales to assess the frequency of symptoms of ocular discomfort?**

FDA Comments: *Acceptable. It is recommended that any visual analog scale be anchored with at least two reference points either in words or pictures.*

No Meeting Comments

7. **Are the proposed secondary endpoints acceptable to FDA?**

FDA Comments: *Acceptable.*

No Meeting Comments

8. **Although Novagali has identified assay of CsA blood levels in the proposed Phase 3 protocol, is this required if Novagali pursues a 505(b)2 pathway with regard to the published body of information on CsA, including information on Restasis (Allergan Pharmaceuticals)?**

FDA Comments: *Independent of whether the application is a 505(b)(1) or a 505(b)(2), there should be an attempt to quantify the amount of systemic absorption that occurs with the drug product .*

A rationale for not conducting pharmacokinetic assessments in the proposed Phase 3 protocol for NOVA22007 should be provided by the Sponsor. The rationale should include supporting preclinical and clinical exposure data (such as the systemic absorption information for NOVA22007 from Phase 2), a comparison of formulations with and without vitamin E, and an assessment of the new formulation demonstrating that changes in the composition would not be expected to significantly alter systemic exposure to CsA.

No Meeting Comments

9. **If Novagali pursues a 505(b)2 pathway with regard to the published body of information on CsA, including information on Restasis (Allergan Pharmaceuticals), is human pharmacokinetic testing required?**

FDA Comments: *Independent of whether the application is a 505(b)(1) or a 505(b)(2), there should be an attempt to quantify the amount of systemic absorption that occurs with the drug product .*

Please refer to the agency's response for Question 8.

No Meeting Comments

10. **If Novagali is required to conduct CsA blood level assay, in how many patients must this testing be performed?**

FDA Comments: *Please refer to the agency's response for Question 8.*

No Meeting Comments

11. **A statistical power of 80% is planned for the proposed pivotal study. Is this adequate in a study intended to support an NDA?**

FDA Comments: *Acceptable.*

No Meeting Comments

REGULATORY PATHWAY

1. **Will FDA consider a 505(b)(2) regulatory pathway for NOVA22007 for the purpose of referencing preclinical information?**

FDA Comments: *Yes.*

No Meeting Comments

2. **Novagali intends to conduct two pivotal phase III studies in similar patient populations, one in the US and one in Europe. Will FDA consider an NDA based on two pivotal studies establishing the superiority of treatment with NOVA22007 over negative control (vehicle)?**

(b) (4)

[redacted]

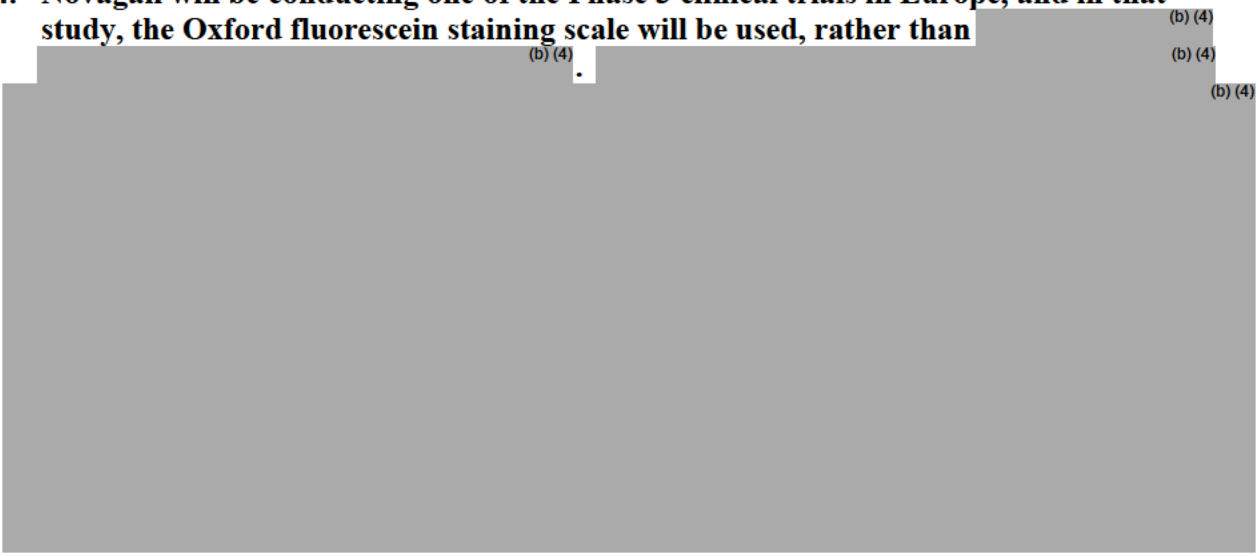
No Meeting Comments

3. Will 6-month safety and efficacy data be adequate to support an NDA?

FDA Comments: *Yes.*

No Meeting Comments

4. Novagali will be conducting one of the Phase 3 clinical trials in Europe, and in that study, the Oxford fluorescein staining scale will be used, rather than (b) (4) (b) (4) (b) (4) (b) (4) .



No Meeting Comments

5. In the absence of reference rights to the approved NDA for Restasis (NDA 50-790), and given that NOVA22007 is a slightly different formulation than Restasis, can the body of non-clinical and clinical data found in the Summary Basis for Approval and in the published literature be used in support of an IND and NDA for NOVA22007?

FDA Comments: *Information in the published literature can be used to support an IND. If the application is submitted as a 505(b)(2), information in the published literature and the agency's conclusions from other NDAs can be used to support a submitted 505(b)(2) NDA. These bodies of information are likely to support the safety, but not the efficacy of a revised ophthalmic formulation of cyclosporine.*

This presumes no use of novel or unapproved excipients in the final formulation. However, you must be able to write the label for the NDA in accordance with the current standards of drug labels.

There is insufficient information provided in the meeting package for the agency to determine the adequacy of the statistical part for the proposed study. We would like to defer our statistical review comments for the protocol until you submit a detailed statistical design and analysis plan.

No Meeting Comments

Additional FDA Comments:
Randomization should include stratification for baseline factors which may significantly impact the outcome.

Visual acuity is both a safety and an efficacy parameter. As such, the Agency believes best corrected visual acuity should be assessed at every visit. At a minimum, the following evaluations are recommended to be performed in each eye and reported separately for each eye (regardless of which eye(s) is treated):

- *Visual acuity (VA), slit lamp, and patient comfort should be performed at every visit.*
- *A slit lamp examination of the anterior segment should include the cornea, conjunctiva, anterior chamber, iris, lids and lashes.*

Endothelial cell counts and dilated fundus examinations should be performed at baseline and at the end of trial in at least one study.

Systemic clinical and laboratory evaluations should be performed at baseline and at the end of the trial in at least one study.

You should explain what is meant by the phrase "baseline ocular sensations".

The "Per-Protocol" analysis should exclude patients with <u>any</u> protocol deviations and should exclude any incomplete patient data from the analysis.

It is recommended that there be a demonstration of a statistically significant difference between the test treatment and vehicle for at least one objective sign and at least one subjective symptom of dry eye. It is recognized that the subjective and objective efficacy findings may not always be able to be demonstrated in the same patients or in the same clinical study.

1. *A number of different endpoints could be potentially acceptable for an objective sign, i.e., corneal staining, tear film breakup time, Schirmer's test score (with or without anesthesia) and for a subjective sign, i.e., a reduction in ocular discomfort, pain, irritation or a reduction in a composite of these or similar symptoms. A statistically significant difference between the mean score of the test product group and the vehicle group for an objective sign and a subjective symptom is acceptable. A statistically significant difference between the percentages of patients achieving a complete resolution of signs and of symptoms is acceptable.*

It is recommended that both an "Intent-to-Treat with the last observation carried forward for missing data" analysis and a "Per-Protocol using only observed data" analysis be submitted. The "Intent-to-Treat" analysis should include all randomized patients. The "Per-Protocol" analysis should exclude patients with <u>any</u> protocol deviations and should exclude any incomplete patient data from the analysis.

Only trial outlines are submitted. When the actual protocols are submitted, they will be reviewed and any additional comments relayed to Novagali Pharma, S.A.

Meeting Comments:

- The Division stated that it is not necessary to identify objective and subjective endpoints, but a statistical correction is required if multiple endpoints are evaluated.
- The Division offered that additional trials could be conducted with a single subjective and single objective endpoint identified in each trial.

Additional Meeting Comments

- Novagali asked if patient follow-up beyond six months is required. The Division responded that it is not.
- Novagali requested clarification of the Division's statement, "The "Per-Protocol" analysis should exclude patients with any protocol deviations and should exclude any incomplete patient data from the analysis." The Division responded that the underline under "any" could be deleted, but that any protocol deviations should be explained.
- The Division stated that it wants to see both Intent-to-Treat and Per-Protocol analyses because these represent the extremes.
- Novagali asked what systemic clinical evaluations should be performed. The Division responded that vital signs should be monitored. In addition, the Division explained that if the application is a 505(b)(2) new drug application, then Novagali could rely on systemic studies of Cyclosporin and would not need to repeat them. However, if the application is not a 505(b)(2) new drug application, then CBC, electrolytes, and hepatic assessment should be included in the trial.
- The Division stated that endothelial cell counts should be taken on at least 100 patients. All patients in one trial and preferably both trials should have dilated fundus examinations at baseline and end-of-treatment.
- Novagali asked the Division for recommendations regarding stratification for baseline factors. The Division suggested stratifying for duration of disease and baseline staining.
- The Division encouraged Novagali to submit questions and proposals for review as they come up during product development.

CONCLUSION: Novagali was in agreement with the Division's responses to their questions.

ACTION ITEMS:

- Novagali will submit their slide presentation to the PIND.

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

/s/

Janice Soreth

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