CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218010Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 120995

MEETING MINUTES

Glaukos Corporation
Attention: Tomas Navratil, PhD
Chief Development Officer, Research and Development
One Glaukos Way
Aliso Viejo, CA 92656

Dear Dr. Navratil:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Travoprost Intraocular Implant. We also refer to the video conference between representatives of your firm and the FDA on November 29, 2022. The purpose of the meeting was to discuss the clinical and statistical data packages for the planned NDA submission.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Dheera Semidey, Senior Regulatory Project Manager at (301) 796-3009.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 29, 2022, from 1pm to 2pm EST
Meeting Location:	Teleconference
Application Number:	IND 120995
Product Name:	Travoprost Intraocular Implant
Indication:	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Sponsor Name:	Glaukos Corporation
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Dheera Semidey, PharmD, RAC

FDA ATTENDEES

Charles Ganley, MD	Director, Office of New Drugs/Office of Specialty Medicine (OND/OSM)
Alex Gorovets, MD	Deputy Director, OND/OSM
Wiley Chambers, MD	Director, Division of Ophthalmology/Office of Specialty Medicine (DO/OSM)
William Boyd, MD	Deputy Director, DO/OSM
Rhea Lloyd, MD	Clinical Team Leader, DO/OSM
Shilpa Rose, MD	Medical Officer, DO/OSM
Martin Nevitt, MD	Medical Officer, DO/OSM
David Summer, MD	Medical Officer, DO/OSM
Milton Sloan, PhD	Drug Product Reviewer, Office of Pharmaceutical Quality/Division of New Drug Products/New Drug Products Branch III (OPQ/DNDP/NDPB-III)
Ping Ji, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP)
Dipak Pisal, PhD	Clinical Pharmacology Reviewer, OCP/DIIP
Judit Milstein	Director, Project Management Staff, Office of Regulatory Operations/Division of Regulatory Operations for Specialty Medicine (ORO/DROSM)
Diana Willard	Chief, Project Management Staff, ORO/DROSM
Dheera Semidey, PharmD, RAC	Regulatory Health Project Manager, ORO/DROSM

SPONSOR ATTENDEES
Tomas Navratil, Ph.D., Chief Development Officer, Research and Development, Glaukos
John Ahn, Sr. Manager, Regulatory Affairs
Nils Hauptmann, VP, Regulatory Affairs
Harsha Sayala, PharmD, Manager, Regulatory Affairs
David Applegate, VP, Commercial Development
Jay Katz, MD, Chief Medical Officer
Dale W. Usner, PhD, VP, Biostatistics and Data Management
Yannan Shen, Manager, Biostatistics
Long Doan, PhD, Sr. Director, Clinical Research

BACKGROUND
Glaukos requested a pre-NDA meeting with the Division to discuss the clinical and statistical portions of their upcoming NDA submission (February 2023). In response to the questions submitted in the October 28, 2022, Meeting Package, the Agency sent preliminary comments on November 17, 2022. On November 22, 2022, Galukos confirmed via email that they would like to have the meeting to discuss Question 7. On November 28, 2022, they provided their responses via email for discussion.

DISCUSSION
For the purposes of this response, the questions submitted in the Meeting Package are in **bold** font, the Division's preliminary comments are in *italics* font, and the meeting discussions are normal font.

BIOSTATISTICS
Question 1: Statistical Analysis Plans for Integrated Summaries
Does the Agency agree that the included anticipated final statistical analysis plans (SAP) for the pooled analyses to be provided in the integrated summary of safety (ISS) and integrated summary of effectiveness (ISE) are adequate and will fully support the NDA submission and review?

FDA Response to Question 1: Acceptable.

Meeting Discussion: None.

Question 2: 120-Day Safety Update Summaries
Does the Agency agree that the proposed 120-Day Safety Update Summaries are adequate and will fully support the NDA review?

FDA Response to Question 2: Your plan is acceptable.

Meeting Discussion: None.

CLINICAL
Question 3: Adequacy of Clinical Efficacy Data

Does the Agency agree that the efficacy results through Month 12 of the two pivotal Phase 3 trials, GC-010 and GC-012, adequately and fully support the submission and review of an NDA with the aim to obtain marketing approval of Travoprost Intraocular Implant, Model G2-TR-125, for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension?

FDA Response to Question 3: Acceptable for submission. Approvability is a review issue.

Meeting Discussion: None.

Question 4: Adequacy of Clinical Safety Data (b) (4)
Does the Agency agree that the safety results of the Phase 2 trial, GC-009, and the 12-month evaluation of the two pivotal Phase 3 trials, GC-010 and GC-012, characterizing the safety (b) (4) **, adequately and fully support the submission and review of an NDA** (b) (4) (b) (4) **with the aim to obtain marketing approval of Travoprost Intraocular Implant, Model G2-TR-125, for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension?**

FDA Response to Question 4: Safety data from the two Phase 3 trials, GC-010 and GC-012, will support submission and review of the proposed NDA. Approvability is a review issue.

Meeting Discussion: None.

(b) (4)

Meeting Discussion: None.

Question 6: Prospectively Collected Corneal Endothelial Cell Data

Does the Agency agree that the corneal endothelial cell data from eyes implanted with the Travoprost Intraocular Implant, that were prospectively collected as agreed previously with the Agency, in the GC-009 Phase 2 trial and the GC-010 and GC-012 Phase 3 trials (b) (4) and IDOS-106-EXCH exchange trial data (b) (4) are adequate to fully support the NDA submission and review?

FDA Response to Question 6: The corneal endothelial cell data from eyes implanted with the Travoprost Intraocular Implant, in Studies GC-009, GC-010, GC-012, and IDOS-106-EXCH exchange trial data (b) (4) will support submission and review of the proposed NDA. Approvability is a review issue.

Meeting Discussion: None.

Question 7: Dislodgement Cases and Corneal Endothelial Cell Data in Eyes with Dislodgements
Does the Agency agree that the information on the implant dislodgement cases, as planned to be provided in the Clinical Study Reports (CSRs), Integrated Summary of Safety, Summary of Clinical Safety, and Clinical Overview of the NDA, which will include detailed narratives as well as corneal endothelial cell data collected after the dislodgement in the study eye and contralateral eye (serving as a fellow eye reference in cases for which the baseline data were not available for the study eye), is adequate and fully supports the NDA submission and review?

FDA Response to Question 7: It is premature to answer this question until the full study reports and narratives have been submitted and reviewed.

Meeting Discussion: Each dislodgement case was evaluated using full ophthalmic examination and specular microscopy. Glaukos proposed to categorize the events as adverse events of device dislocation and not as adverse events of corneal endothelial cell loss. The Agency stated that some cases (e.g., Patients (b) (6)) represent adverse events of corneal endothelial cell (CEC) loss because they demonstrated a clear difference between eyes without a history of prior ocular surgery. The Agency's assumption for such cases would likely be endothelial loss due to dislodgement or explantation. The Agency stated that it is likely that the Agency will consider CEC loss to be probable or suspected if there is a significant loss such as a 30% decrease compared to baseline CEC data though the Agency does not have a firm cutoff. The Agency recommended that data on prior eye surgery be included in the analysis.

Question 8: Adequacy of Clinical Data Package
Does the Agency agree that the outcomes of the Phase 2 GC-009, the two Phase 3 GC 010 and GC-012, and the US IDOS-106-EXCH clinical trials provide adequate evidence of clinical safety and efficacy of Travoprost Intraocular Implant, Model G2-TR-125 to fully support NDA submission for this program?

FDA Response to Question 8: Acceptable for submission. Approvability is a review issue.

Meeting Discussion: None.

LABELING
Question 9: Twelve Month Secondary Efficacy Endpoint
Does the Agency agree that information on the IOP-lowering efficacy of the Travoprost Intraocular Implant, Model G2-TR-125 from the key secondary efficacy endpoint of Month 12 may be included in the Clinical Studies section of the prescribing information?

FDA Response to Question 9: Labeling is a review issue. This question cannot be answered prior to the review of an NDA.

Meeting Discussion: None.

(b) (4)

Meeting Discussion: None.

ISSUES REQUIRING FURTHER DISCUSSION
[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	December 29, 2022

ADDITIONAL INFORMATION
In addition, we note that a multidiscipline pre-submission meeting is scheduled for December 8. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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 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.

MANUFACTURING FACILITIES

[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 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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for

[3] https://www.fda.gov/media/84223/download
[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

commercial production and those used for product and manufacturing process development.

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).[5] 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 Regulations.gov.[6]

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

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] http://www.regulations.gov

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.

ATTACHMENTS AND HANDOUTS

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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
12/20/2022 04:29:13 PM

IND 120995

MEETING MINUTES

Glaukos Corporation
Attention: Tomas Navratil, PhD
Senior Vice President, Research and Development
229 Avenida Fabricante
San Clemente, CA 92672

Dear Dr. Navratil:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Travoprost Intraocular Implant. We also refer to the telecon between representatives of your firm and the FDA on May 9, 2022. The purpose of the meeting was to discuss statistical and clinical considerations for a NDA submission.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Dheera Semidey, Regulatory Project Manager at 301-796- 3009.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 9, 2022, from 3pm to 4pm
Meeting Location:	Teleconference
Application Number:	IND 120995
Product Name:	Travoprost Intraocular Implant
Indication:	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Sponsor Name:	Glaukos Corporation
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Dheera Semidey, PharmD, RAC

FDA ATTENDEES

Alex Gorovets	Deputy Director, Office of New Drugs/Office of Specialty Medicine (OND/OSM)
Wiley Chambers, MD	Director, Division of Ophthalmology/ Office of Specialty Medicine (DO/OSM)
William Boyd, MD	Deputy Director, DO/OSM
Rhea Lloyd, MD	Clinical Team Leader, DO/OSM
David Summer, MD	Medical Officer, DO/OSM
Milton Sloan, PhD	Drug Product Reviewer, Office of Pharmaceutical Quality/Division of New Drug Products/New Drug Products Branch III (OPQ/DNDP/NDPB-III)
Guoxing Soon, PhD	Statistics Team Leader, Office of Biometrics/Division of Biometrics IV (OB/DBIV)
Solomon Chefo, PhD	Statistics Reviewer, OB/DBIV
Ping Ji, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP)
Dipak Pisal, PhD	Clinical Pharmacology Reviewer, OCP/DIIP
Patricia Y. Love, MD, MBA	Deputy Director, Office of Combination Products (OCP)
Judit Milstein	Director, Project Management Staff, Office of Regulatory Operations/Division of Regulatory Operations for Specialty Medicine (ORO/DROSM)
Diana Willard	Chief, Project Management Staff, ORO/DROSM

Dheera Semidey, PharmD, RAC	Regulatory Health Project Manager, ORO/DROSM

SPONSOR ATTENDEES

Tomas Navratil, PhD	Chief Development Officer
Nils Hauptmann	VP, Regulatory Affairs
David Applegate	VP, Commercial Development
Jay Katz, MD	Chief Medical Officer
Dale W. Usner, PhD	VP, Biostatistics and Data Management
Long Doan, PhD	Sr. Director, Clinical Research
Kerry Stephens, OD	VP, Global Clinical Research
Harsha Sayala	Regulatory Affairs Manager
Yannan Shen	Biostatistics Manager

BACKGROUND

Glaukos requested a meeting with the Agency to discuss clinical and statistical questions in preparation for a NDA submission. Their proposed product, travoprost intraocular implant, is surgically implanted to provide an extended release of the product. Though studies were conducted using two different versions of the implant, the difference being the (b) (4), the Sponsor plans on submitting the NDA with the (b) (4), Model G2-TR-125. The NDA submission is planned for Q1 2023.

In response to the questions posted in the April 8, 2022, Meeting Package, the Agency sent preliminary comments on May 4, 2022. On, May 6, 2022, Glaukos provided their responses and requested further discussion of questions 1a, 1b, and to clarify the Agency's Additional Comments on Combination Product Information at the meeting.

DISCUSSION

For the purposes of this response, the questions submitted in the Meeting Package are in **bold** font, the Division's preliminary comments are in *italics* font, and the meeting discussions are normal font.

Question 1

Question 1a: Does the Agency agree that Glaukos' proposed primary efficacy endpoints and analyses, as well as the primary and sensitivity imputation strategies as presented in the draft statistical analysis plan for the pivotal Phase 3 trials, are adequate and acceptable to fully support NDA submission?

FDA Response to Question 1a: Disagree. The primary efficacy endpoint should be fully defined prior to the start of the study. The timepoint options for the change from baseline (CFB) in diurnal IOP in the study eye (i.e., 8AM and 10AM; vs. 8AM, 10AM, and 4PM) at which the primary efficacy analysis will be assessed should be determined prior to the start of the clinical study, not at database lock.

Your primary analysis approach including the proposed missing data and/or intercurrent handling strategies appear reasonable. In addition to the various sensitivity analyses you have outlined in the briefing document, we recommend that a tipping point analysis be performed as additional sensitivity analysis to assess the impact of any potential imbalance in missing data or occurrence of intercurrent events between the treatment groups in the primary analysis.

In Section 9.1 of the briefing document, you specified three options (A, B, and C) for multiplicity adjustment. In option (A), you plan to test noninferiority (NI) of G2-TR-125 to Timolol in the primary efficacy endpoint first. If NI of G2-TR-125 to Timolol is established, then you plan to test:

i. *NI of G2-TR-063 to Timolol in the primary efficacy endpoint* ***and***

ii. *The Key Secondary efficacy endpoint* (b) (4) *: CFB in diurnal IOP in the study eye, at the timepoints chosen for the primary endpoint, at Month 12 will be tested for non-inferiority of G2-TR-125 to Timolol using the same methods and Type I Error (i.e., two-sided 95% CIs).*

Under this option, please clarify if you plan to test items (i) and (ii) above in a hierarchical order. Otherwise, a reasonable multiplicity adjustment plan should be pre-specified for testing these items. The same comment applies for option (B) if you plan to test NI of G2-TR-063 to Timolol in the primary endpoint first.

Regarding your option (C), where you plan to split alpha for NI testing of G2-TR-125 and G2-TR-063 to Timolol in the primary endpoint each at a two-sided alpha = 0.025, we have no objection with your plan. Under this option, your hierarchical testing plan for the key secondary endpoint for the arm for which NI is established is acceptable.

It should be noted that a decision on the primary endpoint evaluation time (6 timepoints vs. 9 timepoints) and the multiplicity adjustment plan should be made prior to patients reach their primary endpoint time at Month 3.

Meeting Discussion: With respect to the primary endpoint including 6 vs 9 time points, the Agency commented that the primary efficacy endpoint should have been determined prior to the start of the study. The Agency stated that the Sponsor may use 6 or 9 timepoints, but those timepoints need to be selected as soon as possible.

Question 1b: Does the Agency agree that Glaukos' proposed secondary efficacy endpoints and analyses, as well as the primary and sensitivity imputation strategies as presented in the draft statistical analysis plan for the pivotal Phase 3 trials, are adequate and acceptable to fully support NDA submission?

FDA Response to Question 1b: You have not specified a multiplicity adjust plan for testing both G2-TR-125 and G2-TR-063 to Timolol in the secondary efficacy

endpoints. Thus, in the absence of a reasonable multiplicity adjustment plan, we would not consider the secondary efficacy endpoints supportive of efficacy.

Meeting Discussion: Glaukos proposed two hierarchical fixed-sequence testing strategies, both of which they believe effectively will control Type I error at a 2-sided alpha = 0.05 among the primary and secondary endpoints while accounting for testing both G2-TR-125 and G2-TR-063, using 2-sided 95% CIs at each level. They would only move on to the next level of testing if non-inferiority is demonstrated at the previous level.

The Agency agreed that the strategies proposed by the Sponsor were acceptable in regard to multiplicity. However, the Agency recommended make a decision as soon as possible on which arm, G2-TR-125 or G2-TR-063 will be tested first.

Question 2: Does the Agency agree that the proposed clinical data package, based on the outlined set of clinical trials and their respective biostatistical analyses, is adequate to support the NDA submission for Travoprost Intraocular Implant, Model G2-TR-125, for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension?

FDA Response to Question 2: The proposed clinical data package appears adequate to file an NDA submission.

Meeting Discussion: None.

Question 3: Does the Agency agree that the integrated summary of safety (ISS), based on the identified clinical trials to be included, is acceptable to fully support the NDA submission?

FDA Response to Question 3: Your plan to include safety information from your Phase 2 trial and 2 Phase 3 trials in the Integrated Summary of Safety is acceptable.

Meeting Discussion: None.

Question 4: Does the Agency agree that the integrated summary of efficacy (ISE), based on the identified clinical trials to be included, is acceptable to fully support the NDA submission?

FDA Response to Question 4: Your proposal for the Integrated Summary of Efficacy (ISE) is acceptable. However, efficacy should be demonstrated in each trial separately.

Meeting Discussion: None.

Question 5: Does the Agency agree that the proposed data cutoff strategy for the safety and efficacy data beyond 12 months, proposed to be applied to the two

ongoing pivotal Phase 3 clinical trials, is acceptable to fully support the NDA submission?

FDA Response to Question 5: Agree. The proposed data cutoff strategy for the safety and efficacy data beyond 12 months is acceptable for filing. The adequacy of the 12-month data will be a review issue.

Meeting Discussion: None.

Question 6: Does the Agency agree that the proposed summaries included in the ISS and ISE are acceptable for the planned NDA submission?

FDA Response to Question 6: Agree.

Meeting Discussion: None.

Question 7: Does the Agency agree that the proposed subgroup analyses within the ISS and ISE are acceptable for the planned NDA submission?

FDA Response to Question 7: Agree.

Meeting Discussion: None.

Question 8: Does the Agency agree that the proposed imputation strategies for the ISE are acceptable for the planned NDA submission?

FDA Response to Question 8: Agree.

Meeting Discussion: None.

Question 9: Does the Agency agree that the proposed MedDRA and WHO-Drug versions are acceptable for the planned NDA submission?

FDA Response to Question 9: Acceptable.

Meeting Discussion: None.

Question 10: Does the Agency agree that the proposed Data Standardization Plan, including SDTM and ADaM (and corresponding implementation guide [IG]) and controlled terminology [CT] versions are acceptable for the planned NDA submission?

FDA Response to Question 10: Agree.

Meeting Discussion: None.

AD HOC Question:
Glaukos would like to pose one additional question related to the Agency's "Additional Comments: Combination Product Information".
Given the continued changes in the regulation of drug device combination products, what is the best process for Glaukos to reach 100% clarity on the specification and testing requirements fully supporting iDose NDA, which is near term, for both iDose pharmaceutical drug product and medical device components? Could the Agency elaborate on the roles and responsibilities of Office of Combination Products, CDER and CDRH in this process? Thank you so much for any further guidance from the Agency on this topic.

Meeting Discussion: The Agency clarified that once their NDA is submitted, it would come to CDER as the lead center. CDER will consult CDRH as needed and any comments or information requests from CDRH would come through CDER.

The Sponsor's product is considered a combination; however, if the Sponsor disagrees, then they would need to contact the Office of Combination Products (OCP) to determine which center would be the lead.

The Sponsor proposed to submit a meeting request with device information for CDRH review and comments. The Agency acknowledged that they would review any information the Sponsor submits.

ADDITIONAL COMMENTS: Combination Product Information

On April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued its decision in *Genus Medical Technologies LLC v. U.S. Food and Drug Administration*, 994 F.3d 631 (D.C. Cir. 2021). The *Genus* court stated "[e]xcepting combination products…devices must be regulated as devices and drugs — if they do not also satisfy the device definition — must be regulated as drugs." In implementing this decision, FDA has determined that the language in § 200.50(c) indicating that ophthalmic dispensers are regulated as drugs when packaged with ophthalmic drugs is now obsolete, because these articles meet the *device* definition. Accordingly, in reference to the Agency additional comments in the IND meeting minutes of January 19, 2022, your product is a single entity combination product under 21 CFR 3.2(e)(1). Should you have questions on the product classification, you may contact the Office of Combination Products at combination@fda.gov.

- Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. As provided in the March 2022 FDA guidance for *Certain Ophthalmic Products: Policy Regarding Compliance*

With 21 CFR Part 4 Guidance for Industry[1] the Agency explained its implementation plan for current approved products and those with pending marketing applications. Please refer to this guidance document for additional information regarding compliance with the requirements in part 4 (21 CFR part 4) for ophthalmic drugs packaged with eye cups, eye droppers, or other dispensers. Should you have additional questions, please submit them to the IND. Also, in the interim as the Agency continues to develop its implementation plans, for further information on 21 CFR Part 4, the final rule is accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. Also, Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (Jan. 2017), is accessible at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

- For location of information on the device constituent part see the FDA eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" October 2021* accessible at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf

- In your future submission, the Form FDA 356h should identify your product as a combination product (see form field 24). Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.

- For general information on discussing the combination product and its constituent parts, see FDA guidance on *Requesting FDA Feedback on Combination Products* (December 2020) accessible at https://www.fda.gov/media/133768/download

Post-Meeting Comment: For general information on combination products see Combination Products | FDA

ISSUES REQUIRING FURTHER DISCUSSION
No issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date

[1] https://www.fda.gov/media/157067/download.

Meeting Minutes	FDA	June 8, 2022

ATTACHMENTS AND HANDOUTS

Attachment 1: Glaukos Responses to FDA Preliminary Comments

ADDITIONAL INFORMATION

PRESCRIBING INFORMATION

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

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

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[4] and the guidance for industry, *Identification of Manufacturing Establishments in*

[4] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[5]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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).[6] 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 Regulations.gov.[7]

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.

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[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[7] http://www.regulations.gov

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.

7 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
05/18/2022 01:00:29 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120995

MEETING MINUTES

Glaukos
Attention: Jeff Wells, Pharm.D., MBA, RAC
Senior Vice President, Clinical, Regulatory, and Quality Affairs
229 Avenida Fabricante
San Clemente, CA 92672

Dear Dr. Wells:

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

We also refer to the meeting between representatives of your firm and the FDA on December 3, 2017. The purpose of this End of Phase 2 meeting was to obtain guidance from the Agency on the proposed Phase 3 clinical and overall development plan for travoprost intraocular implant in patients with primary open-angle glaucoma or ocular hypertension.

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

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, 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

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 4, 2017
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	120995
Product Name:	travoprost intraocular implant
Indication:	primary open-angle glaucoma or ocular hypertension
Sponsor Name:	Glaukos
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Diana Willard

FDA ATTENDEES

Wiley Chambers, M.D.	Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd, M.D.	Clinical Team Leader, DTOP
Rhea Lloyd, M.D.	Clinical Reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Yunfan Deng, Ph.D.	Statistical Reviewer, OB/DBIV
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.	Acting Product Quality Team Leader, Office of Product Quality (OPQ)/New Drug Products Branch III (NDRBIII)
Sithamalli Chandramouli, Ph.D.	Product Quality Reviewer, OPQ/NDRB III
Banu Zolnik, Ph.D.	Biopharmaceutics Reviewer, OPQ/ONDP/DB/Branch 1

Kesia Alexander, Ph.D.	Scientific Deputy Director, Center for Devices and Radiological Health (CDRH)/Office of Device Evaluation (ODE) /Division of Ophthalmic and ENT Devices (DOED)
Claudine Krawczyk	Engineering Reviewer, CDRH/ODE/DOED/Intraocular and Corneal Implants Devices Branch (ICIB)
Jennifer Brown	Microbiology Reviewer, CDRH/ODE/DOED/ICIB
Simona Bancos, Ph.D.	Biocompatibility Reviewer, CDRH/ODE/DOED/ICIB
Damia Jackson	Regulatory Project Manager, CDRH/ODE/DOED
Dheera Semidey, Pharm.D.	Regulatory Project Manager, DTOP
Wendy Streight, Pharm. D.	Regulatory Project Manager, DTOP
Diana Willard	Chief, Project Management Staff, DTOP

GLAUKOS ATTENDEES

Jeff Wells	Sr. Vice President, Clinical, Regulatory, and Quality Affairs
David Haffner	Sr. Vice President, Product Development
Gabriella Szekely, Ph.D.	Vice President, Translational Sciences
Nina Nguyen	Sr. Director, Regulatory Affairs
Eugenia Thomas, O.D.	Sr. Director, Clinical Research and Medical Affairs
L. Jay Katz, M.D.	Chief Medical Officer

GLAUKOS CONSULTING ATTENDEES

(b) (4)

BACKGROUND

A September 27, 2017, submission from Glaukos requested an End of Phase 2 meeting to obtain guidance from the Agency on the proposed Phase 3 clinical and overall development plan for travoprost intraocular implant in patients with primary open-angle glaucoma or ocular hypertension. An October 6, 2017, Meeting Request Granted letter listed December 4, 2017, as the agreed upon meeting date.

The November 21, 2017, Meeting Package was received on November 22, 2017, Meeting Preliminary Comments were sent to Glaukos on November 29, 2017. A November 30, 2017, e-mail from Glaukos requested clarification of the Agency's comments for questions 2a and the "ADDITIONAL AGENCY COMMENTS" provided in the November 29, 2017, Meeting Preliminary Comments document. The responses e-mailed to Glaukos on November 30, 2017, are in Attachment 1.

A December 1, 2017, e-mail from Glaukos, contained Glaukos' responses to the Agency's Meeting Preliminary Comments. This e-mail further stated that "... we are most interested in discussing some of the clinical/statistical responses – specifically 2, 4b, 6, and 7."

DISCUSSION

Following, in **bold font**, are the questions in the November 21, 2017, Meeting Package, the November 29, 2017, FDA responses to these questions are in *italic* font, the Glaukos December 1, 2017, comments are in ***bold italic font***, and meeting discussion is in regular font.

CLINICAL

Efficacy Results from Phase 2 Study

1. **Does the agency agree that clinical safety data presented in the 3-Month Clinical Report from the U.S. Phase 2 trial (Attachment 1) provides sufficient support for an expanded investigation of the travoprost implants G2TR-063 and G2TR-125 in a Phase 3 trial?**

   FDA Response: Yes.

   Glaukos December 1, 2017, Response: FDA answer is clear.

   Meeting Discussion: None

Phase 3 Trial Design - Dose Selection/Endpoint

2.a. Does the agency agree with the proposed dose selection and endpoint (primary and secondary), (b) (4) in these Phase 3 trial designs?

FDA Response: The proposed dose selection, primary and secondary efficacy endpoints and analyses which assess data through the Week 12 endpoint are acceptable. The (b) (4) (b) (4) *are not acceptable.*

We recommend that you include the mean IOP change from baseline at each time point for each post-baseline visit as a secondary endpoint; we also recommend you analyze this efficacy measure using the analysis of covariance method adjusted for baseline IOP values.

Glaukos December 1, 2017, Response: We agree to include the mean IOP change from baseline at each post-baseline visit as a secondary endpoint and will also include this in the covariate analysis by baseline IOP values.

We require further clarification regarding the agency's objection (b) (4) (b) (4)***. Does the agency agree that*** (b) (4)***analysis of the data through Week 12 is appropriate for the primary efficacy endpoint? If so, which of the following summaries*** (b) (4)***does the agency believe are appropriate:***

(b) (4)

Meeting Discussion: The Agency stated that it is acceptable to adjust the baseline using data collected in the first 12 weeks. The basic issue is whether individual measurements from multiple timepoints are aggregated. From the information submitted, it seems plausible that within the first 12 weeks there will be sufficient information to evaluate if this product is efficacious for the proposed indication. The issue then becomes the duration of use. The Agency recommends additional timepoints to better document the duration of effect of this product in enrolled subjects. There is a need to understand at what point there is no longer the same efficacy.

The Agency recommended picking a time at which all enrollees would return for IOP assessment. Any comparison with timolol needs to be in comparison to both the peak and trough of timolol's efficacy. There does not need to be a peak and trough established for every patient at every visit.

The Agency noted that information pertaining to Glaukos' proposed (b) (4) (b) (4) is unlikely to be included in the labeling.

At least two clinical trials are recommended as the current proposal involves a new regimen for travoprost in addition to being a change of dosage form.

Rescue Medication

2.b. Does the agency agree with the rescue medication approach?

FDA Response: Yes. It is acceptable to specify that rescue medication may be used at the investigator's discretion rather than only after a prespecified IOP measure is reached as long as the investigator documents the clinical findings and reason for needing to prescribe the rescue medication.

Glaukos December 1, 2017, Response: FDA answer and comments are clear.

Meeting Discussion: None

Phase 3 Trial Procedures

3. Does the agency agree with the proposed procedure exclusions and frequencies for these Phase 3 trials?

FDA Response: No. Specifically, the following proposed changes are not acceptable: (b) (4)

Glaukos December 1, 2017, Response: FDA answer and comments are clear. Glaukos will amend the Phase 3 protocol GC-010 to (b) (4) ***specify that all adverse events, both ocular and systemic, will be followed to resolution. The amended Phase 3 protocol, GC-010, will be submitted in the forthcoming IND information amendment.***

Meeting Discussion: None

Masking and Comparator Design

4.a. Does the agency agree with the proposed comparator (placebo/sham group) and masking scheme for the Phase 3 program?

FDA Response: Timolol and artificial tears are acceptable comparators. However, it is unacceptable to retain some (b) (4) *bottle caps. To minimize bias, the bottle caps of all study medications should be the same color.*

Glaukos December 1, 2017, Response: Timolol and artificial tears are acceptable comparators. However, it is unacceptable to retain some (b) (4) ***bottle caps. To minimize bias, the bottle caps of all study medications should be the same color.***

Meeting Discussion: None

(b) (4)

(b) (4)

Meeting Discussion: None

Proposed Efficacy Comparisons

5. Does the Agency agree with the proposed (b) (4)

(b) (4)

FDA Response: No. See response to Question 2a.

Glaukos December 1, 2017, Response: Please see Glaukos' response to FDA comments on Question 2a.

Meeting Discussion: None

Sample Size and Statistical Plan

6.a. Does the agency agree with the proposed statistical plan (within Protocol Attachment 2) to support the NDA?

FDA Response: No. See response to Question 2a.

We have the following additional comments:

- *Please specify how you plan to control the overall type I error rate for comparing two testing arms with the active control timolol. We recommend you refer to the draft guidance "Multiple Endpoints in Clinical Trials Guidance for Industry" (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf) for feasible multiplicity adjustment approaches.*
- *Because there is no better way to handle missing data than preventing the data to be missed, we strongly recommend that all possible measures be taken to minimize missing data and collect efficacy and safety data at each scheduled study visit for subjects who discontinue the study drug early or who receive rescue medication.*
- *We recommend that you include the mean IOP change from baseline at each time point for each post-baseline visit as a secondary endpoint; we also recommend you analyze*

this efficacy measure using the analysis of covariance method adjusted for baseline IOP values.

- *As part of sensitivity analyses, for missing IOP data because of adverse event(s), concomitant medication use, or rescue medication use, we recommend you impute the missing values using corresponding baseline data.*

Glaukos December 1, 2017, Response: ***The study as currently designed more than adequately controls type I error. The requirement for study success is that the sequential hypotheses described in section 9.4.4.2 of the protocol will be met for either of the two elution rates versus the control. There are two opposing factors that will affect the type I error rate of the overall testing procedure:***

- ***The first is that, in order to succeed for either elution rate, there are multiple hypothesis tests that must succeed: nine in Step A, and five of the nine in Step B. This reduces the experiment-wise type I error rate substantially below the $\alpha = 0.025$ that is used for each individual hypothesis test.***
- ***The second is that there are two different elution rates that are being tested against a single control, this increases the type I error rate somewhat (see, e.g., Dunnett JASA 1955).***
- ***Of the two factors, the first far outweighs the second.***

The situation is further complicated by potential correlations between measurements for an individual subject and by the interrelations between hypothesis tests in Step A and Step B. However, unless the correlation between measurements within a patient is quite high (higher than 0.99) the first factor is still dominant. Note that in the Phase 2b study, the correlation between IOP measurements within a subject was approximately 0.50.

Given the complexity of the situation, the type I error for the study was calculated using simulation. Even with within-subject correlations as high as 0.95, the experiment-wise type I error rate is approximately 0.001.

All measures will be taken to avoid missing data, and IOP measurements will be collected whenever possible and as associated with adverse events or concomitant/rescue medication use. For the sensitivity analyses, Glaukos would like to clarify "missing" IOP data as being non-collection of an IOP measurement; in these cases missing IOP data will be imputed with the baseline IOP value for the corresponding baseline measurement time.

Meeting Discussion: Glaukos noted that under the proposed analysis, 9 sequential non-inferiority hypotheses tests must succeed in Step A and 5 of 9 must succeed in Step B. The Agency stated their belief that each hypothesis is an independent entity and if each individual test is below the $\alpha = 0.025$, that is acceptable. The Agency requested that Glaukos submit their explanation for proposed statistical plan plus the code to the IND for review.

Site Enrollment

6.b. Does FDA agree that sites completing enrollment in one Phase 3 trial can be moved to the other Phase 3 trial? Is there any limit on the number of subjects that a single

investigator can contribute to the pivotal trial? Is there any limit on the proportion of data in the pivotal trial coming from OUS sites?

FDA Response: Safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials. Independence refers to different investigators and different geographic locations.

The Agency does not recommend that investigators be permitted to enroll subjects in both Phase 3 trials. To maintain study independence, investigators should enroll subjects for only one of the Phase 3 trials. It is recommended that the clinical sites be apportioned to each study geographically, such as sites east of the Mississippi River in one study and sites west of the Mississippi River in the second study.

While there is no limit on the number of subjects that a single investigator may contribute, no single investigator/site should enroll a proportion of subjects sufficient to dominate a trial's outcome.

There is no limit on the proportion of foreign trial data that may be used to support a NDA or BLA. Foreign data may support the basis of approval for an application provided the criteria described in 21 CFR 314.106 are met, including that the foreign data is applicable to the U.S. population and U.S. medical practice.

Glaukos December 1, 2017, Response: FDA answer and comments are clear.

Meeting Discussion: None

Diurnal IOP Measurements

7. Are diurnal IOP measurements required (b) (4)

(b) (4)

FDA Response: No, diurnal IOP measurements are not required (b) (4)

(b) (4)

(b) (4)

Meeting Discussion: The Agency referred back to the Meeting Discussion for 2.a., and the recommendation for at least two studies. (b) (4)
(b) (4)

NONCLINICAL

Nonclinical Data

8. Does the FDA agree that the nonclinical data package described in Section 9 is adequate for registration?

FDA Response: Yes, your completed nonclinical studies appear adequate to support a 505(b)(2) NDA. Please be aware that if the formulation or impurities change, or the clinical trials identify unexpected safety concerns, then we may recommend additional nonclinical testing to address these specific concerns.

a. *You state (Volume 1, page 70 of 375) that the* (b) (4) *will be eliminated for Phase 3 and this does not constitute a change* (b) (4) *While we agree that this seems to be a minor change in the manufacturing of the titanium container, we recommend that you provide justification that the elimination of the* (b) (4) *step in the manufacturing of the titanium container does not impact its biocompatibility.*

(b) (4)

Meeting Discussion: None

b. *You state (Volume 1, page 72 of 375) that the* (b) (4) *vendor for the* (b) (4) *inserter components will be changed as compared to the inserter used in Phase 2. However, it is not clear whether these components have direct or indirect contact with*

the patient. If the (b) (4) *inserter components directly contact the patient or the titanium container, we recommend that you provide evidence demonstrating that the change in vendor does not impact the biocompatibility of the inserter. This is important since using the same materials from different vendors may change the material specification and introduce new impurities in the inserter materials.*

Glaukos December 1, 2017, Response: ***The*** (b) (4) ***inserter components have no direct contact to the patient or titanium container.***

Meeting Discussion: The Agency requested that Glaukos submit documentation demonstrating that the (b) (4) inserter components have no direct contact to the patient or titanium container.

(b) (4)

Meeting Discussion: None

PRODUCT QUALITY

Specifications, Acceptance Criteria & Methods

9. Does the agency agree that these specifications, acceptance criteria and methods, provide sufficient control of product purity, identity, safety, potency and quality for Phase 3?

FDA Response: The proposed specifications seem reasonable at this stage of development. For an NDA submission, additional tests and/or tightening of the specification may be required.

We have the following recommendation as your drug development proceeds towards an NDA:

a. Tighten the assay acceptance criteria to (b) (4)
b. With respect to the drug release test, based on the provided information, it appears that the in vitro drug release profile is incomplete and the drug's release rate decreases with time indicating possible lack of sink conditions; therefore, the proposed in vitro drug release method may not be appropriate for your proposed drug product. We recommend that you investigate the drug release characteristics of your proposed product using other testing equipment, such as USP Apparatus 4 or modified USP Apparatus 7.

We request that you provide the in vitro drug release development and validation report including the following information/data:

1) *Detailed description of the in vitro drug release method being proposed for the evaluation of your proposed drug product and the developmental parameters (e.g., selection of the equipment/apparatus, in vitro release media, agitation/rotation/dips speed, pH, assay, sink conditions, etc.) used to select the proposed in vitro drug release method as the optimal test for the product. Clearly specify the testing conditions used for each test. The drug release profile should be complete or cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend the use of at least twelve samples per testing variable and sampling time points.*
2) *The initial phase of drug release should be adequately covered for characterization of the burst release and at days 1, 2, 4, 6 etc. for characterizing the subsequent drug release profile. Provide the complete drug release data (individual, mean, SD, profiles) for the product. Report the drug release data as the cumulative percentage of drug released with time (the percentage is based on the product's label claim). You may also report the rate of release.*
3) *You may consider the development of an accelerated drug release method to be used as the QC method for your proposed drug product. Please note that the accelerated drug release method should mimic the long-term drug release profile, but in a shorter time period (e.g., 2-3 days).*
4) *Submit data supporting the discriminating ability of the proposed in vitro drug release method. In general, the discriminating ability of the selected method should compare drug release profiles of the proposed drug product (reference) and the test products that are intentionally manufactured with meaningful variation for the most relevant critical material attributes and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). For example, for the proposed drug product, investigate factors affecting initial burst release.*
5) *Provide supportive validation data for the in vitro drug release method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*
6) *For the selection of the in vitro drug release acceptance criteria of the product, consider the following points:*
   i. *The drug release profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the acceptance criteria of your product (i.e., criteria-sampling time point and limits).*
   ii. *The acceptance criteria should be established based on average in vitro drug release data for each lot under study, equivalent to USP Level 2 testing (n=12).*
   iii. *A minimum of three time points is recommended to set the specifications. These time points should cover the initial, middle, and terminal phases of the drug release profile. The last time point should be where at least (b) (4)% of drug is released. If the maximum amount released is less than (b) (4)%, the last time point should be the time when the plateau of the release profile has been reached.*
   iv. *In general, the selection of the acceptance criteria ranges is based on mean target value ±10% and > (b) (4)% for the last criteria time-point. Include a detailed*

discussion of the justification of the proposed acceptance criteria in the appropriate section of the NDA

We recommend that you submit the in vitro drug release development/validation report for your proposed drug product under an Amendment to your IND. Please indicate in the Amendment's cover page that you are requesting FDA's feedback, specifically from the Division of Biopharmaceutics/ONDP/OPQ.

***Glaukos December 1, 2017, Response:* FDA answer and recommendations are clear. Glaukos will take into consideration FDA's recommendation as listed above as our drug development proceeds towards NDA. Glaukos will submit the in vitro drug release development/validation report via an IND Amendment for FDA's review and feedback when the development/validation report is complete.**

Meeting Discussion: None

Stability Program

10. Does the agency agree the proposed stability program will support registration and to set an expiration date for the drug product?

FDA Response: The proposed stability program seems reasonable. However, we remind that you follow ICH Q1A(R2) guidance for stability. We expect the NDA at the time of submission should provide at least 12 months of long-term and 6-months accelerated stability data for three registration batches in the intended commercial configuration. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified.

***Glaukos December 1, 2017, Response:* FDA answer and comments are clear. Glaukos will execute the stability program as proposed in the Briefing Package as summarized below: Implants will be stored without regard to orientation because the formulation is filled (b) (4) and is always in contact with all product contact surfaces of the primary container system.**

Registration Stability Program		
Study	**Storage Condition**	**Minimum time period covered by data at NDA submission**
Long-term	5 °C ± 3°C / uncontrolled RH	12 months
Intermediate (Optional Long-term)	25°C ± 2°C / 60% RH ± 5% RH	6 months or optional 12 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

Meeting Discussion: Regarding the proposed stability program, the Agency noted that the stability conditions are for high humidity and stated that for ophthalmics, The Agency recommended that the stability studies be conducted at 25°C/40%RH and 40°C/25%RH.

Drug Substance Specifications

11. Does the agency agree the drug substance specifications listed on the manufacturers C of A and Glaukos' internal testing are sufficient for registration?

FDA Response: Your proposal appears reasonable for the IND. Ensure that the drug substance specification is in alignment with the DMF holder's specification. We acknowledge that you plan to reference DMF no. (b) (4) *You should perform additional tests that you propose in the IND specification, if it is not included in the manufacturer's CoA.*

Final acceptability of the drug substance specification will be determined during the review of the NDA.

For ease of review, at the time of NDA submission we request that you include the following information for drug substance under Module 3:

- *a. A summary of drug substance properties under 3.2.S.1.3,*
- *b. A tabular summary of any specified drug substance impurities under 3.2.S.3.2,*
- *c. The current release specifications for the drug substance under 3.2.S.4.1,*
- *d. An analysis of three representative batches of drug substance under 3.2.S.4.4 (any drug substance lots used to manufacture the exhibit drug product lots should also be included in this summary), and*
- *e. The current drug substance retest period and storage conditions under 3.2.S.7.1.*

We also recommend that you consult with the DMF holder to ensure that a copy of the letter of authorization (LOA) is included under the DMF.

Glaukos December 1, 2017, Response: FDA answer and recommendations are clear.

Meeting Discussion: None

Phase 3 Stability Protocol

12. Does the agency agree that the proposed stability program is acceptable to support the Phase 3 clinical studies?

FDA Response: The proposed stability program for the Phase 3 clinical studies seems reasonable.

Glaukos December 1, 2017, Response: ***FDA answer and comment are clear.***

Meeting Discussion: None

Demonstrating Equivalency for Commercial Manufacturing

13. Does the agency agree that the plan demonstrates equivalency of the drug product and that no additional non-clinical or clinical studies are required?

FDA Response: No, we do not agree. We recommend that you include the drug products manufactured at the commercial site in the clinical trial(s).

Glaukos December 1, 2017, Response: ***FDA answer and recommendations are clear. Glaukos will include as part of the Phase 3 clinical trial drug products manufactured at both the clinical manufacturing site*** (b) (4) ***and the intended commercial manufacturing site*** (b) (4)

Meeting Discussion: None

GENERAL

Initiate Phase 3 Trial

14. Based on the presented information, does the agency agree that Glaukos can begin the initiation of the Phase 3 trials?

FDA Response: We recommend that you respond to the following:

1. *For the Phase 3 implant as compared to the Phase 2 implant, you describe* (b) (4) (b) (4) (b) (4) *. Prior to initiation of the Phase 3 study, we recommend you perform additional testing to verify and validate the durability* (b) (4) *since the* (b) (4) *has changed.*

   Glaukos December 1, 2017, Response: FDA answer and recommendations are clear. Prior to initiation of Phase 3 study, Glaukos will perform additional testing to verify and validate the durability (b) (4) ***as a result of the change*** (b) (4) (b) (4) ***. The testing and durability validation results will be submitted via IND Amendment prior to the initiation of Phase 3 study.***

   Meeting Discussion: None

2. *In addition, you state that* (b) (4) (b) (4)

(b) (4)

However, you do not indicate how this (b) (4) *will impact the final overall length of the implant. Please clarify how this change impacts the final overall length for the Model G2TR-125. Please address concerns that may arise regarding implant clearance within the anterior chamber of the eye due to the* (b) (4) *dimensions.*

Glaukos December 1, 2017, Response: ***The*** (b) (4) ***overlaps with the length of the implant. The final overall length of the Model G2TR-125 implant has not changed. Please see below for detailed picture of the Model G2TR-125 implant:***

(b) (4)

Meeting Discussion: The Agency acknowledged Glaukos' reply and stated that it is acceptable.

FORWARD LOOKING QUESTION

(b) (4)

(b) (4)

Meeting Discussion: None

ADDITIONAL AGENCY COMMENTS

Only a protocol synopsis is presented in the briefing package. Additional comments will be forthcoming when the full protocols and statistical analysis plans are submitted.

Glaukos December 1, 2017, Response: ***The full Phase 3 Protocol GC-010 and statistical analysis plan was submitted in the Briefing Package in Attachment 2 of Volume 2. The full Phase 3 Protocol GC-010 and statistical plan will be submitted again in the forthcoming IND Amendment.***

Meeting Discussion: None

ADDITIONAL MEETING DISCUSSION:

The Agency asked whether the applicant planned to recommend leaving the implant in place after the drug product had been depleted. Glaukos stated that the goal would be (b) (4) (b) (4). In studies conducted in Armenia, the implant had been explanted. The Agency noted that the label should state what is planned to occur with the implant (b) (4) (b) (4)

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/s/

WILEY A CHAMBERS
12/17/2017