

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**218010Orig1s000**

**NON-CLINICAL REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

|                                |                                                                                                                            |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Application number:            | 218010                                                                                                                     |
| Supporting document/s:         | SDN0001 (eCTD SN 0001)                                                                                                     |
| Applicant's letter date:       | 02-22-2023                                                                                                                 |
| CDER stamp date:               | 02-22-2023                                                                                                                 |
| Product:                       | iDose® TR (Travoprost Intraocular Implant)                                                                                 |
| Indication:                    | Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension                                   |
| Applicant:                     | Glaukos Corporation                                                                                                        |
| Review Division:               | Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURN/SM) |
| Reviewer:                      | Muriel Saulnier, DVM, PhD, DABT                                                                                            |
| Acting Supervisor/Team Leader: | Kimberly Hatfield, PhD                                                                                                     |
| Division Director:             | Mukesh Summan, PhD, DABT                                                                                                   |
| Project Manager:               | Lois Almoza                                                                                                                |

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

Glaukos Corporation (Glaukos) has submitted an original New Drug Application (NDA) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Travoprost Intraocular Implant, 75 µg (Model G2-TR-125), a drug led drug-device combination product. The implant is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) and will rely on the Agency's previous findings of safety (i.e., nonclinical studies not conducted by or for Glaukos) for the listed drug (LD) Travatan® (travoprost ophthalmic solution) 0.004%, approved under NDA 021257. Travatan® was discontinued but not for an efficacy or safety reason.

Travoprost Intraocular Implant is a sterile, drug-eluting implant that is surgically delivered through a clear corneal incision (intracameral) and anchored in the anterior chamber angle of the eye. The implant elutes travoprost drug substance formulated with (b) (4). The predicted elution duration is 30-36 months in patients.

To obtain approval, Glaukos is relying on the results of clinical studies GC-010 and GC-012, where patients received a single intracameral injection of one implant that was kept for 36 months, and of clinical study IDOS-106-EXCH, which is an extension study after removal of the first implant at Month 36 followed by intracameral injection of a second implant that was then left for 12 supplementary months. Clinical trial IDOS-106-EXCH also served to assess the marketed product as changes were made to the manufacturing process of the original implant. This “bridge” methodology between the two different manufacturing processes was agreed upon with the Agency at a Type C meeting held on 06-07-2021 (See Regulatory Background).

At the conclusion of multiple pre-IND/pre-NDA meetings (see Regulatory Background), the Agency confirmed that the nonclinical package appeared adequate to support a 505(b)(2) NDA submission, pending review.

In conformance with ISO 10993 requirements, the Sponsor conducted biocompatibility testing of the drug releasing titanium reservoir (with titanium cap and EVA membrane without the drug), the EVA membrane, and the stainless-steel inserter tip that enters the eye. Safety review of biocompatibility studies is deferred to CDRH.

## 1.2 Brief Discussion of Nonclinical Findings

The preclinical development of Travoprost Intraocular Implant included Sponsor's performed non-Good Laboratory Practices (GLP) studies (i.e., a primary pharmacology and toxicity study in cynomolgus monkeys, and an ocular pharmacokinetics study in New Zealand White rabbits, and GLP studies (i.e., an ocular distribution and safety study in New Zealand White rabbits and a 6-month toxicity study in Yucatan Miniature Swine (minipigs)). All studies were performed with the implant administered by intracameral injection.

During development, the drug product label claim for the travoprost content of Travoprost Intraocular Implant Including Model G2-TR-125 was updated to 75 µg (from (b) (4)). A quality information amendment was submitted to the IND correcting the values (IND 120995, Sequence Number 0046). The original preclinical reports reviewed by Dr. McDougal in DO, still referred to Travoprost Intraocular Implant ((b) (4)) although the actual drug product value was about 75 µg.

*This reviewer's comment: For this NDA submission, the change in label claim from (b) (4) to 75 µg content in the drug product in the device had no impact on the outcomes of the pharmacology and toxicology review.*

For genotoxicity, carcinogenicity and reproductive and developmental toxicity, the Sponsor will rely on the LD.

### PHARMACOLOGY

No new pharmacology studies were conducted by the Sponsor. Travoprost effects on the eye are well known. Travoprost free acid, a prostaglandin analog, is a selective false positive (FP) prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

The Sponsor undertook a proof-of-concept study with the implant in the monkey. In that species, the therapeutic target concentration of (b) (4) was mostly achieved and maintained for up to 1 year in the aqueous humor with no drug accumulation, corresponding to a mean intraocular pressure reduction of 4.8 mmHg relative to baseline at Month 12.

### PHARMACOKINETICS/TOXICOKINETICS

In humans, the absorption, distribution, metabolism, and excretion (ADME) profile of travoprost is well understood.

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites *via* beta-oxidation of the  $\alpha$  (carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, *via* oxidation of the 15-hydroxyl moiety, as well as *via* reduction of the 13,14 double bond.

The elimination of travoprost free acid from the plasma is rapid and levels are generally below the limit of quantification within one hour after dosing. Less than 2% of the topical ocular dose of travoprost is excreted in the urine within 4 hours as the travoprost free acid.

Glaukos established the ocular pharmacokinetic profile of the Travoprost Intraocular Implant in the rabbit, by measuring the total free acid (TFA) levels in the ocular tissues and blood after intracameral implantation with G2-TR-125, 75  $\mu$ g. In all pharmacokinetic evaluations, TFA levels in the aqueous humor, the tissue of interest, showed mostly sustained, relatively constant release of the drug product that remained at the therapeutic target concentration of (b) (4) for at least 6-7 months (end of the studies), whereas the systemic exposure to TFA was below the lower limit of quantitation of 0.2 ng/mL at all time points analyzed.

### TOXICITY

Ocular toxicity studies of the Travoprost Intraocular Implant were performed in the rabbit and the minipig. In the rabbit, one G2-TR-125 Travoprost Intraocular Implant (b) (4) containing 75  $\mu$ g travoprost was injected in the anterior angle chamber of the right eye of each animal and the left eye was left untreated. In the minipig, the protocol was similar to the rabbit's protocol except that two implants were injected in one eye compared to the untreated contralateral eye. The implants were well tolerated in both studies for up to 6 months (end of the studies). Based on the sustained release of the drug product at a constant rate for at least 6 months in the animals and in humans, the toxicity data resulted in clinical ocular safety margins of 1X and 2X with the rabbit and the minipig ocular NOAELs (based on dose comparison), respectively, while the clinical systemic safety margin was 1.36X with the minipig systemic NOAEL (no systemic NOAEL defined in the rabbit for lack of data), assuming that the patient may receive one implant *per eye*.

*This reviewer's comment: The toxicity of the implant by intracameral injection was estimated in an ocular distribution study in the New Zealand White rabbit (Study 14C94Q1R1G62) and an ocular toxicity study in the minipig (Study CB14-5048-P-TX). Both studies were performed in GLP conditions. In both protocols, the implants were kept until the end of the studies at 6-month post-implantation, hence*

*these studies did not include recovery periods. In both studies, the animals were sacrificed at several time points across the course of the study which resulted in too few animals analyzed per time point as the number was less than the recommended number of 4 non rodents per gender to obtain meaningful data. In addition, as the rabbit study was a pharmacokinetic study rather than a toxicity study, limited end points were analyzed. In particular, no histopathology of the eyes/adnexa and/or systemic tissues were included in the rabbit PK study protocol such that no systemic NOAEL could be derived from the rabbit study. Study drug was well-tolerated though. Also, the ocular pharmacokinetics of travoprost was not studied in the minipig. It is nevertheless assumed that there was sustained release of the drug product at a constant rate for at least 6 months in that species as well, as it was demonstrated in both a rabbit and a monkey study, and in clinical trials with the Implant. Furthermore, as the toxicity of travoprost on the eye is well understood, the absence of a recovery period in the animal studies was acceptable.*

### **1.3 Recommendations**

#### **1.3.1 Approvability**

Pharmacology/toxicology supports approval of iDose® TR (Travoprost Intraocular Implant, 75 µg) despite some limitations of the nonclinical program.

Interpretation of the preclinical findings was limited by the suboptimal designs of the toxicity studies (i.e., not enough number of animals at each necropsy, lack of recovery periods in both studies, no tissues analyzed by histopathology for either ocular or systemic rabbit studies, lack of sensitivity of the method for measuring TFA levels in the animal studies). In addition, compared to the systemic NOAEL in the minipig, the clinical systemic safety margin was less than 10X, and was not supportive of the clinical dose. The safety margin could only be derived by dose comparison due to the lack of sensitivity of the analytical method used by the Sponsor in the pig study (Lower Level of Quantitation (LLOQ); 200 pg/mL nonclinical studies compared to 10 pg/mL clinical studies), which produced plasma levels below LLOQ and that could not be compared to clinical exposures. Safety margins based on dose were also low due to limitations of dose administration in the animal – more than 2 implants per eye in the minipig may have been infeasible in the study so only a maximal dose of 150 µg could be achieved. However, the ocular safety margins of 1X and 2X were found to be acceptable by this reviewer, since the ocular toxicity of travoprost is well known due to previous clinical experience of Travatan, and the implants were left for 6 months without obvious toxicity findings.

To establish a systemic safety bridge with the LD, the Sponsor compared the clinical systemic exposure to TFA after the implant was placed in one eye of patients vs the LD applied to each eye and demonstrated that plasma exposure from the implant was lower than the LD. Also, the clinical pharmacology team determined by review that this scientific bridge to the LD Travatan was acceptable with 1 implant in one eye or, 1 implant in each eye (see Clinical Pharmacology review by Liping Pan).

Based on this clinical pharmacology bridge, the sponsor may rely on the LD Travatan and previous findings of nonclinical safety of the Travatan product as described in labeling.

### **1.3.2 Additional Non-Clinical Recommendations**

None.

### **1.3.3 Labeling**

Proposed edits to product labeling are addressed under a separate review.

## **2 Drug Information**

### **2.1 Drug**

CAS Registry Number  
157283-68-6

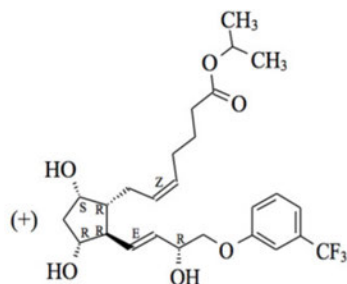
Generic Name  
Travoprost Intraocular Implant

Code Name  
G2-TR-125 or G2-TR

Chemical Name  
[1*R*-[1*α*(*Z*),2*β*(1*E*,3*R*<sup>\*</sup>),3*α*,5*α*]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1 - butenyl]cyclopentyl]-5-heptenoic acid, 1 methylethylester

Molecular Formula/Molecular Weight  
C<sub>26</sub>H<sub>35</sub>F<sub>3</sub>O<sub>6</sub>/500.55

## Structure or Biochemical Description



Pharmacological Class  
Prostaglandin F analog

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

- Izba<sup>1</sup> (Travoprost), NDA #204822, travoprost ophthalmic solution, 0.003%, for the reduction of elevated IOP in patients with OAG or OHT, discontinued (Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons), Novartis, approval 2014.

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<sup>1</sup>[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/204822s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204822s002lbl.pdf)  
(Label revised 2021)

- Travatan<sup>2</sup> (Travoprost), NDA #021257, travoprost ophthalmic solution, 0.004%, for the reduction of elevated IOP in patients with OAG or OHT, discontinued (Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons), Alcon pharms ltd, first approval 2001. This product was chosen as the LD by the Sponsor.

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<sup>2</sup>[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/021257s025lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021257s025lbl.pdf)  
(Label revised 2011)

- Travatan z<sup>3</sup> (Travoprost), NDA #021994, travoprost ophthalmic solution, 0.004%, for the reduction of elevated IOP in patients with OAG or OHT, prescription, Novartis, approval 2006.

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<sup>3</sup>[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/021994s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021994s013lbl.pdf)  
(Label revised 2020)

- Travoprost: Multiple ANDAs; solution/drops; ophthalmic, for the reduction of elevated IOP in patients with OAG or OHT, multiple Sponsors.

- IND 120995 (Travoprost Intraocular Implant, 75 µg, Glaukos) for which the pharmacology and toxicology (PT) was reviewed by Dr. McDougal, former FDA employee in support of the Division of Ophthalmology. Review archived in DARRTs on 12-17-2015<sup>4</sup>.

<sup>4</sup>[https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af803c4edb&\\_afRedirect=2828081257311034](https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af803c4edb&_afRedirect=2828081257311034)

The Sponsor produced Letters of Authorization (LoA) for Travoprost drug substance, supplied by (b) (4) and supported by DMF # (b) (4) Ethylene Vinyl Acetate Copolymer, VitalDose® (b) (4) supplied by Celanese Canada ULC. and supported by DMF # 037444.

## 2.3 Drug Formulation

The Travoprost Intraocular Implant is composed of a titanium reservoir (or container) with a titanium anchor, containing approximately 75 µg of travoprost drug substance formulated with (b) (4) (Table 1).

The titanium reservoir is sealed with an ethylene vinyl acetate (EVA) membrane held in place with a titanium crimp cap. The EVA membrane (b) (4) and contains (b) (4) vinyl acetate. The EVA membrane, which is in direct contact with the travoprost drug product formulation filled into the titanium reservoir, allows drug to elute through the membrane at a controlled rate for an expected duration of 30-36 months. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter. An inserter is used to facilitate placement of the implant by the physician. The inserter handpiece is made from common medical grade (b) (4), and the material of the inserter tip that enters the eye is stainless steel. The implant filled with the drug product is loaded onto the inserter.

Table 1: Quantitative Composition of Travoprost Bulk Drug Product

| Ingredient                       | Composition (%) |
|----------------------------------|-----------------|
| Travoprost (USP), drug substance | (b) (4)         |
|                                  | (b) (4)         |

(Copied from 3.2.P.1. Drug Product)

The assembled implant and inserter are placed in a (b) (4) blister tray that is sealed with a Tyvek lid. The sealed tray is placed together with

an oxygen absorber packet into a transparent barrier pouch (b) (4) which is sealed and placed in a unit carton. The unit cartons are (b) (4) the final labeling contents are added within the unit carton (i.e., prescribing information and patient card) (Table 2).

Table 2: Travoprost Intraocular Implant Components (up to the Tertiary Packaging)

| Component                       | Drug Product Constituent | Medical Device Constituent Implant | Medical Device Constituent Inserter | Primary Container Closure | Secondary Packaging | Tertiary Packaging | Material                                                                                                                                                                            |
|---------------------------------|--------------------------|------------------------------------|-------------------------------------|---------------------------|---------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Travoprost Drug Substance       | X                        |                                    |                                     |                           |                     |                    | Travoprost                                                                                                                                                                          |
| (b) (4)                         | X                        |                                    |                                     |                           |                     |                    | (b) (4)                                                                                                                                                                             |
| Titanium Reservoir              |                          | X                                  |                                     |                           |                     |                    | Titanium, (b) (4)                                                                                                                                                                   |
| EVA Membrane                    |                          | X                                  |                                     |                           |                     |                    | Ethylene vinyl acetate                                                                                                                                                              |
| Titanium Cap                    |                          | X                                  |                                     |                           |                     |                    | Titanium, (b) (4)                                                                                                                                                                   |
| Inserter                        |                          |                                    | X                                   |                           |                     |                    | stainless steel, (b) (4)                                                                                                                                                            |
| Blister Tray                    |                          |                                    |                                     | X                         |                     |                    | (b) (4)                                                                                                                                                                             |
| Tyvek Lid                       |                          |                                    |                                     | X                         |                     |                    | Tyvek (b) (4)                                                                                                                                                                       |
| Radiation Indicator             |                          |                                    |                                     |                           | X                   |                    | (b) (4)                                                                                                                                                                             |
| O <sub>2</sub> Absorbing Packet |                          |                                    |                                     |                           | X                   |                    |                                                                                                                                                                                     |
| Barrier Pouch                   |                          |                                    |                                     |                           | X                   |                    |                                                                                                                                                                                     |
| Carton                          |                          |                                    |                                     |                           |                     | X                  | The unit carton contains the barrier pouch packaging, prescribing information, patient card and label for the unit carton. A tamper evident seal is affixed to both ends of carton. |

(Copied from 3.2.P.1. Drug Product)

## 2.4 Comments on Novel Excipients

From the review of IND120995<sup>4</sup> by Dr. McDougal:

**EVA filter**

- The Sponsor submitted biocompatibility studies for the EVA filter which review is deferred to CDRH
- The EVA filter during clinical use will contact the aqueous humor without directly contacting the ocular tissues
- The Sponsor performed a 6-month GLP toxicity study assessing the travoprost intraocular implant in minipig that qualified the use of EVA in intracameral location
- The Sponsor cited multiple device uses of EVA, which include larger amounts of EVA than G2-TR-125 placed in the eye

(b) (4)

**2.5 Comments on Impurities/Degradants of Concern*****Drug Substance (DS)***

The Sponsor referred to (b) (4) DMF # (b) (4) and their Letter of Authorization allowing the FDA to review (b) (4) DMF and to permit Glaukos to cross-reference the DMF. Information on travoprost organic impurities, named in the USP Monograph on travoprost and also observed during synthesis, as well as elemental impurities and residual solvents were described in Section 3.2.S.3.2 of the NDA submission. The Sponsor confirmed that travoprost DS does not contain (b) (4) and no new impurities exist in their drug substance.

***Drug Product (DP)***

Glaukos reviewed the available information from its suppliers of materials for the constituents of its drug product Travoprost Intraocular Implant, as well as the manufacturing process for the drug product. Glaukos concluded that there is negligible potential for the formation of (b) (4) impurities from the components of the drug product and from the process of manufacturing the drug product. Glaukos has also concluded that there is negligible potential for impurities in the drug product derived from (b) (4) and elemental impurities from the titanium and other components of the drug product.

***Leachables Studies***

A 36-month leachable study is ongoing. As only volatile organic compounds (VOCs) were found in the device constituents and container closure system components, Glaukos validated an analytical method for VOCs and monitored G2TR VOC leachables during the stability studies of the registration batches. Lots were stored at 25°C/40% relative humidity (RH) and 40°C/25% RH. Data for leachables are available for up to 12 months. To date, no leachables have been identified in any Travoprost Intraocular Implant container closure components.

## 2.6 Proposed Clinical Population and Dosing Regimen

Draft Labeling Text located in Module 1.14.1.3.



## 2.7 Regulatory Background

- A Type B pre-IND meeting between the firm and the Agency occurred on March 28, 2014 (Minutes archived in DARRTS on 04/22/2014<sup>5</sup>) to discuss the CMC, preclinical and clinical development of Travoprost Intraocular Implant, (b) (4) for the reduction of intraocular pressure (IOP) in primary OAG or OH, two versions of the device being developed, both having an EVA membrane filter (b) (4) (code names G2TR-63 and G2TR-125).

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<sup>5</sup>[https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8032b50a&\\_afRedirect=2887396328694913](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8032b50a&_afRedirect=2887396328694913)

- The Original IND 120995 was submitted on 11-18-2015 for a prospective, randomized phase II study comparing two elution rates of Glaukos Travoprost Intraocular Implants, 75 µg (corrected from (b) (4)), to timolol maleate ophthalmic solution, USP, 0.5%. In this protocol which involved one study eye in each participant, patients received either one implant model G2TR-063 + placebo drops, or one implant model G2TR-125 + placebo drops, or sham surgery + timolol maleate ophthalmic solution 0.5%, twice daily (8 am and 8 pm) for 3 years. A Study May Proceed Letter was not found in DARRTS although the clinical reviewer judged the opening clinical protocol “acceptable” (review archived in DARRTS on 01-06-2016<sup>6</sup>).

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<sup>6</sup><https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af803c8795>

- A Type B End of Phase 2 pre-IND meeting between the firm and the Agency took place on December 03, 2017 (Minutes archived in DARRTS on 12/17/2017<sup>7</sup>) to obtain guidance from the Agency on the proposed Phase 3 clinical trial and overall development plan for Travoprost Intraocular Implant in patients with primary OAG or OH. At this meeting the firm asked for nonclinical and clinical input including if FDA agreed that the nonclinical data package was adequate for registration. FDA responded that it was, as long as the formulation and impurities continued to be qualified, and the clinical trials did not identify new safety concerns.

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<sup>7</sup>[https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af80471cde&\\_afRedirect=2890966580859628](https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af80471cde&_afRedirect=2890966580859628)

- A Type C teleconference meeting with the Agency was held on March 20, 2020, to discuss the ongoing Phase 3 chemistry, manufacturing, and controls (CMC) development activities, and the registration stability batches and process validation plan for Model G2TR-125. Preliminary FDA comments were received on March 12, 2020, and Glaukos provided responses to FDA preliminary comments on March 17, 2020, requesting further discussion on Questions 2a, 4, 6, 7 and 9 (not reproduced herein). During the March 20, 2020, Type C meeting, the additional feedback and agreement with FDA was captured in notes taken by Glaukos and acknowledged by FDA (Memorandum of Meeting Minutes dated April 15, 2020<sup>8</sup>). Notably, at this meeting, the Sponsor asked if the Agency agreed that the proposed plan to demonstrate equivalence of the product between Phase 3 and registration lots was adequate, and that no further nonclinical data or clinical data were required to which FDA answered that the to-be-marketed product, including the to-be-marketed inserter, should be included in at least one of the clinical trials

supporting the safety and efficacy of the product. Preclinical was not invited/involved in the discussion.

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<sup>8</sup><https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af80557b43>

- Subsequently, Glaukos sought to obtain confirmation and further guidance on the discussion outcome from the March 20, 2020, Type C meeting. This was the subject of a meeting on June 7, 2021, which included preclinical representatives, where Sponsor asked the Agency to confirm the adequacy of their preclinical plan for an NDA submission type 505(b)(2) (Meeting Minutes dated June 25, 2021<sup>9</sup>). The pharmacology and toxicology (PT) discipline concurred with the Sponsor and added that all impurities, leachables and extractables in Travoprost Intraocular Implant should be qualified at the time of the NDA submission. The acceptability of the data would be a review issue. There was no further discussion of the preclinical development plan. Nevertheless, Glaukos asked again to confirm the prior agreement obtained at the Type C meeting held on March 20, 2020, i.e., that the manufacturing changes of the drug product, representative of the final manufacturing process and the final to-be marketed drug product (both the implant and inserter of the Travoprost Intraocular Implant), were sufficiently qualified in the US exchange clinical trial (IDOS-106 EXCH) for an NDA submission, to which the clinical team responded affirmatively.

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<sup>9</sup><https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af805fcde1>

(b) (4)



### 3 Studies Submitted

#### 3.1 Studies Reviewed

*Studies reviewed by Dr. McDougal in IND 120995<sup>4</sup>:*

*Final Report of G2TR Monkey Clinical Study, and Discussion of Applicability to Human Feasibility Clinical (not numbered)*

*CB14-5048-P-TX: A 6-Month Toxicity Study Assessing the Travoprost Intraocular Implant in Minipigs*

*12C94Q3R2: Evaluation of the pharmacokinetics of the Sponsor's test article in the eyes of male New Zealand White rabbits*

*14C94Q1R1G62: Ocular Distribution and Safety of the Sponsor's Test Article After Implantation in the Eyes of Male and Female New Zealand White Rabbits*

*Study reviewed by this reviewer:*

*16C95Q2: 7-Month Ocular Pharmacokinetic Study in Rabbits*

#### 3.2 Studies Not Reviewed

*Analytical Methods and Validations Reports*

*08-104: Bioanalytical Report for the Exploratory Analysis of Travoprost and Travoprost Acid in Monkey Aqueous Humor*

#### 3.3 Previous Reviews Referenced

IND 120995

Salient features of the review of IND 120995<sup>4</sup> by Dr. McDougal at FDA were reproduced herein. For the details, the reader is invited to refer to the DARRTs archived pharmacology and toxicology review of IND120995<sup>4</sup>.

### 4 Pharmacology

#### 4.1 Primary Pharmacology

*Mechanism of action*

From Travatan® PI, 2011<sup>2</sup>

Travoprost, a synthetic analog of prostaglandin F2 $\alpha$ , is an isopropyl ester prodrug hydrolyzed by esterases in the cornea to its biologically active free acid. Travoprost free acid is a selective FP prostanoid receptor agonist which reduces IOP by increasing uveoscleral outflow.

*This reviewer's comment: During the pre-IND interactions, in his review of IND 120995<sup>4</sup> Dr McDougal indicated concurrence with the Sponsor that no primary (proof of concept) or secondary pharmacology testing was necessary with the implant.*

## **4.2 Secondary Pharmacology**

There were no studies conducted by the Sponsor.

## **4.3 Safety Pharmacology**

There were no studies conducted by the Sponsor.

The Sponsor justified not conducting safety pharmacology studies since systemic exposure to travoprost free acid (TFA) after the administration of the Travoprost Intraocular Implant was below the lower limit of quantitation (LLOQ, 10 pg/mL) in humans (Study GC-009), and higher systemic exposures were reported in patients treated with Travatan® eye drops ( $C_{\max} = 0.018 \pm 0.007$  ng/mL) without systemic or safety pharmacological findings (Denis, 2007; Travatan® PI<sup>2</sup>).

# **5 Pharmacokinetics/ADME/Toxicokinetics**

## **5.1 PK/ADME**

*Studies conducted by the Sponsor*

Nonclinical pharmacokinetic studies of travoprost and TFA distribution consisted of a non-GLP 28-day ocular pharmacokinetic study in New Zealand White (NZW) rabbits (Study 12C94Q3R2), a non-GLP 7-month ocular pharmacokinetic study in NZW rabbits (Study 16C95Q2), a GLP 6-month ocular toxicity and pharmacokinetic study in NZW rabbits (Study 14C94Q1R1G62), and a non-GLP 12-month ocular pharmacodynamic and pharmacokinetic study in cynomolgus monkeys (Bioanalytical Report 08-104, Dose Medical Final Report).

### ABSORPTION

The Sponsor indicated (and this reviewer agrees) that the absorption of travoprost ester pro-drug through the cornea and its rapid conversion into TFA was well established for Travatan®.

The Travoprost Intraocular Implant delivers travoprost directly into the anterior chamber and no additional absorption studies were conducted.

DISTRIBUTION

*This reviewer's comment: Note that in the original IND 120995 submission, some of the Sponsor's studies in animals evaluated the rates of travoprost elution in the ocular structures, based on (b) (4) two different EVA membranes of the implant, (b) (4) (b) (4) ). The Travoprost Intraocular Implant type G2TR-125 was chosen for further development.*

Studies reviewed by Dr. McDougal in IND 120995<sup>4</sup>

12C94Q3R2: 28-Day Ocular Pharmacokinetic and Tolerability Study in Rabbits

#### Methods

Two G2-TR-125 Travoprost Intraocular Implants (75 µg (corrected from (b) (4)) travoprost/per implant; (b) (4) EVA membrane) were implanted into the anterior chamber angle of the right eye of male New Zealand White (NZW) rabbits euthanized at Day 14 and Day 28 days (6-7/timepoint). Aqueous humor, ocular tissues (lens, ICB, retina, choroid, sclera, and cornea) and blood/plasma were harvested and analyzed to establish the concentrations of TFA.

#### Study design

| Dose group | Dose route                       | N | Treatment                                          |                   |             |                                                                                                         |
|------------|----------------------------------|---|----------------------------------------------------|-------------------|-------------|---------------------------------------------------------------------------------------------------------|
|            |                                  |   | Right eye                                          | Left eye          | Time points | Matrices collected                                                                                      |
| 1          | Intracameral Ocular Implantation | 7 | Travoprost Intraocular Implant G2-TR-125 75 µg x 2 | Untreated Control | Day 14      | Blood/<br>Plasma                                                                                        |
| 2          | Intracameral Ocular Implantation | 6 | Travoprost Intraocular Implant G2-TR-125 75 µg x 2 | Untreated Control | Day 28      | Treated eye only: Aqueous humor, vitreous, lens, iris/ciliary body, retina, choroid, sclera, and cornea |

#### Results

At Day 14, aqueous humor (AH) TFA levels had a mean of 4.78 ng/mL and ranged from 2.41-8.32 ng/mL (5.3 to 18.1 nM) while at Day 28, AH TFA levels had a mean of 5.03 ng/mL and ranged from 1.66-9.01 ng/mL (3.6-19.6 nM). In 11 out of 13 animals, AH TFA levels were near the therapeutic target level (b) (4) (Faulkner 2010).

The exposures in other ocular tissues were generally below the limit of quantitation (BLOQ) or near the Lower Limit of Quantitation (LLOQ) of 2 ng/g for tissues homogenates and 0.2 ng/mL for fluids, with the exception of the iris/ciliary body (ICB), cornea and sclera in the order ICB > cornea > sclera = aqueous humor > choroid (not detected in the retina or lens). Travoprost and TFA were not detectable (< 0.2 ng/mL) in any of the plasma samples (Tables 3, 4).

Table 3: Travoprost Free Acid Concentrations in Aqueous Humor from the Non-GLP 28-Day NZW Rabbit Pharmacokinetic Study

| Individual Animal Values for Travoprost Free Acid in Aqueous Humor |       |         |          |       |         |
|--------------------------------------------------------------------|-------|---------|----------|-------|---------|
| Day 14                                                             |       |         | Day 28   |       |         |
| Animal #                                                           | ng/mL | nM      | Animal # | ng/mL | nM      |
| 1080                                                               |       | (b) (4) | 1075     |       | (b) (4) |
| 1065                                                               |       |         | 1074     |       |         |
| 1069                                                               |       |         | 1073     |       |         |
| 1076                                                               |       |         | 1072     |       |         |
| 1077                                                               |       |         | 1067     |       |         |
| 1078                                                               |       |         | 1066     |       |         |
| 1079                                                               |       |         |          |       |         |
| Average                                                            | 4.78  | 10.4    |          | 5.03  | 10.9    |
| Standard Deviation                                                 | 2.79  | 6.1     |          | 3.47  | 7.6     |

BLOQ = Below Limit of Quantitation (< 0.2 ng/mL)

(Copied from the PT review of IND 120995<sup>4</sup> on p 34)

Table 4: Travoprost Free Acid Concentrations in Ocular Tissues from the Non-GLP 28-Day Ocular Pharmacokinetic Study in Rabbits

| Tissue            | Average Concentration (SD)<br>ng/mL or ng/g* |              |
|-------------------|----------------------------------------------|--------------|
|                   | Day 14                                       | Day 28       |
| Aqueous humor**   | 4.78 (2.79)                                  | 5.03 (3.47)  |
| Iris/Ciliary body | 27.6 (26.1)                                  | 16.8(4.28)   |
| Vitreous humor    | BLOQ                                         | BLOQ         |
| Retina            | 2.23 (NC)                                    | BLOQ         |
| Sclera            | 5.20 (2.05)                                  | 4.57 (1.97)  |
| Cornea            | 17.1 (21.7)                                  | 11.0 (2.48)  |
| Lens              | BLOQ                                         | BLOQ         |
| Choroid           | BLOQ                                         | 2.90 (0.441) |

BLOQ = Below Limit of Quantitation (< 0.2 ng/mL for AH and VH, < 2 ng/g for other tissues)

SD = Standard deviation, NC= not calculated, due to limited data

\* Values are in ng/mL for aqueous and vitreous humor and ng/g for all other tissues

\*\* The pilot study animal value was used for the AH result for 14-day results (n = 7); all other tissue values are n = 6

(Copied from the PT review of IND 120995<sup>4</sup> on p 42)

*14C94Q1R1G62: Ocular distribution and safety of the Sponsor's test article after implantation in the eyes of male and female New Zealand White rabbits*

Methods

TFA ocular distribution and ocular toxicity of Travoprost Intraocular Implants in NZW rabbits at Days 7, 28, 90 and 181 (3/sex/timepoint) following implantation of one G2-TR-125 Travoprost Intraocular Implant (75 µg (corrected from (b) (4)) travoprost; (b) (4) membrane) in the anterior chamber angle of the right eye were evaluated. The left eye was untreated. Blood and ocular tissues from the right eye (AH, ICB, cornea, conjunctiva, lens, vitreous humor, retina, choroid, sclera) were collected. TFA levels from these samples were determined by using the validated LC-MS/MS method.

Study design

| Group | N    |        | Treatment (OD)                   | Treatment (OS)    | Dose (µg/implant) | Termination time point | Matrices collected                                                                                                             |
|-------|------|--------|----------------------------------|-------------------|-------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------|
|       | Male | Female |                                  |                   |                   |                        |                                                                                                                                |
| 1     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 7                  | Blood (for plasma)                                                                                                             |
| 2     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 28                 | Treated eye (OD) only: aqueous humor, vitreous humor, lens, iris/ciliary body, retina, choroid, sclera, conjunctiva and cornea |
| 3     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 90                 |                                                                                                                                |
| 4     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 181                |                                                                                                                                |

## Results

TFA ocular concentrations were highest on Day 7 and generally lower between Day 28 through Day 90, and slightly increased by Day 181 for AH and ICB samples. In AH, the implant resulted in measurable TFA concentrations from Day 7 (17.58 ng/mL) through Day 180 (4.33 ng/mL). From Day 28 through Day 180, AH TFA levels were maintained in the range of 1.65-4.33 ng/mL (3.6-9.4 nM), which was within the target therapeutic level of (b) (4). In the ICB and cornea, TFA concentrations of 20.93 ng/g and 37.80 ng/g, respectively, were observed on Day 7, and exposures were maintained at a lower range from Day 28 through Day 180. Measurable TFA concentrations in ICB, a target tissue for Travoprost Intraocular Implant, were maintained at the level of at least 6 ng/g through Day 180.

There was no quantifiable TFA (< 2 ng/g) in lens, retina, choroid and vitreous humour (< 0.2 ng/mL) samples, with the exception of one sample on Day 28 and one on Day 90, with levels near the LLOQ. TFA was detected in sclera and conjunctiva of some rabbits at earlier time points and was mostly below the LLOQ (< 0.2 ng/g) in conjunctiva by Day 90 and in sclera by Day 181. TFA plasma concentrations were below the LLOQ (< 0.2 ng/mL) in all rabbits, indicating minimal exposure of TFA in the systemic circulation (Table 5).

Table 5: Travoprost Free Acid Concentrations in Ocular Tissue in the GLP 6-Month Ocular Toxicity and Pharmacokinetic Study in NZW Rabbit

| Tissue                   | Average (SD) Concentration [ng/mL (humors) or ng/g (tissues)] |             |             |             |
|--------------------------|---------------------------------------------------------------|-------------|-------------|-------------|
|                          | Day 7                                                         | Day 28      | Day 90      | Day 180     |
| <b>Aqueous humor</b>     | 17.58 (7.92)                                                  | 4.20 (7.18) | 1.96 (1.15) | 4.33 (2.22) |
| <b>Vitreous humor</b>    | BLOQ                                                          | 0.239 (NC)  | 0.238 (NC)  | BLOQ        |
| <b>Retina</b>            | BLOQ                                                          | BLOQ        | BLOQ        | BLOQ        |
| <b>Sclera</b>            | 3.89 (1.30)                                                   | 2.68 (0.37) | 3.34 (1.22) | 2.89 (NC)   |
| <b>Cornea</b>            | 37.80 (20.79)                                                 | 9.83 (9.02) | 3.99 (2.68) | 8.44 (9.66) |
| <b>Lens</b>              | BLOQ                                                          | BLOQ        | BLOQ        | BLOQ        |
| <b>Choroid</b>           | BLOQ                                                          | BLOQ        | BLOQ        | BLOQ        |
| <b>Iris/Ciliary body</b> | 20.93 (6.55)                                                  | 6.95 (3.29) | 9.27 (2.49) | 8.60 (3.92) |
| <b>Conjunctiva</b>       | 3.86 (1.11)                                                   | 4.06 (2.29) | 5.88 (4.48) | 3.19 (0.23) |

BLOQ = Below Limit of Quantitation

NC = Not calculated

SD = Standard deviation

(Copied from the PT review of IND 120995<sup>4</sup> on p 35)

*Bioanalytical Report 08-104, Dose Medical Final Report: 12-Month Ocular Pharmacodynamic and Pharmacokinetic Study in Monkeys*

### Methods

The ocular distribution of travoprost TFA was evaluated in a 12-month ocular pharmacokinetic study in 4 female cynomolgus monkeys that were previously screened as “travoprost IOP responders”, before intracameral injection of a 25 µg G2-TR-036 implant model, representative of the Travoprost Intraocular Implant (b) (4) to accommodate the smaller ocular anatomy of the anterior chamber of the cynomolgus monkey’s eye. The G2-TR-036 implants were designed to be (b) (4) of the G2-TR-063 and G2-TR-125 Travoprost Intraocular Implants and were determined to have an *in vitro* elution rate of (b) (4).

IOP was measured weekly and AH samples were collected for travoprost and TFA analysis at 2 months pre-implantation, on the day of implantation (Day 0) and at 6, 15, 20, 26, 31, 38, 44, 50, 54 weeks after implantation, and 4 and 9 weeks after explantation at week 54.

### Results

AH travoprost concentrations were below the LLOQ in all samples (< 0.2 ng/mL) at all time points, due to the conversion of travoprost to TFA. Mean AH TFA concentrations were BLOQ (< 0.1 ng/mL), prior to implantation, and ranged from 4.45 ng/mL (9.7 nM) at 6 weeks after implantation to 1.03 ng/mL (2.2 nM), at 54 weeks after implantation, and were BLOQ at 4 and 9 weeks after explantation. The results indicated that AH TFA concentrations were near the therapeutic target concentration of (b) (4) and were maintained for up to 1 year with no drug accumulation, corresponding to mean IOP reduction at 1 year of 4.8 mmHg relative to the pre-dose baseline IOP (Table 6).

Table 6: Aqueous Humor Travoprost and Travoprost Free Acid Concentrations and Intraocular Pressure in the 12-Month Ocular Pharmacodynamic and Pharmacokinetic Study in Monkeys

| Sampling Date (MM/DD)<br>(Study Day)   | AH Travoprost<br>Concentration<br>ng/mL | AH Travoprost Free Acid<br>Concentration<br>ng/mL (nM)<br>(Mean ± SD) | IOP Decrease (mmHg)<br>from Baseline<br>(26.1 mmHg)<br>(Mean) |
|----------------------------------------|-----------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------|
| 6/11 (2 mos pre-op)                    | BLOQ                                    | BQL (as expected)                                                     | ---                                                           |
| 8/11 (surgery day)                     | BLOQ                                    | BQL (as expected)                                                     | ---                                                           |
| 10/11 (6 wks post-op)                  | BLOQ                                    | 4.45 (9.7)                                                            | ---                                                           |
| 12/11 (15 wks post-op)                 | BLOQ                                    | 1.71 (3.7)                                                            | ---                                                           |
| 1/12 (20 wks post-op)                  | BLOQ                                    | 5.00 (10.9)                                                           | ---                                                           |
| 2/12 (26 wks post-op)                  | BLOQ                                    | 2.20 (4.8)                                                            | 5.2                                                           |
| 3/12 (31 wks post-op)                  | BLOQ                                    | 4.19 (9.1)                                                            | 5.2                                                           |
| 5/12 (38 wks post-op)                  | BLOQ                                    | 1.80 (3.9)                                                            | 5.3                                                           |
| 6/12 (44 wks post-op)                  | BLOQ                                    | 1.43 (3.1)                                                            | ---                                                           |
| 8/12 (50 wks post-op)                  | BLOQ                                    | 1.09* (2.4)                                                           | 4.8                                                           |
| 9/12 (54 wks post-op)                  | BLOQ                                    | 1.03* (2.2)                                                           | ---                                                           |
| 10/12 (4 wks post-explant)             | BLOQ                                    | BQL (as expected)                                                     | ---                                                           |
| 11/12 (9 wks post-explant)             | BLOQ                                    | BQL (as expected)                                                     | ---                                                           |
| Average Oct-June<br>(Aug-Sep excluded) | BLOQ                                    | 2.97                                                                  | ---                                                           |
| <b>Average</b>                         |                                         |                                                                       | <b>5.1</b>                                                    |

\*Aug-Sept drug levels likely influenced by exhaustion of one or more implants.

AH – aqueous humor; BLOQ – Below limit of quantitation; IOP – intraocular pressure

(Copied from Module 2.6.4. Pharmacokinetics Written Summary on p 12)

Study reviewed by this reviewer

#### 16C95Q2: 7-Month Ocular Pharmacokinetic Study in Rabbits

##### Methods

One Travoprost Intraocular Implant containing 75 µg of travoprost (G2-TR-063 and G2-TR-125 implants (b) (4)) was administered by intracameral injection in the right eye of NZW rabbits (8/sex/implant arm). The left eye was untreated. AH tap samples were collected on Days 29, 73 and 179, and AH and ICB were collected on Days 8, 30, 180, or 211 for LC-MS/MS analysis of TFA.

## Study design

| Group | Treatment                      |                      | N                                                | Sacrifice Time Point                                                     | Matrices collected                                                                                                                                                                     |
|-------|--------------------------------|----------------------|--------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|       | OD                             | OS                   |                                                  |                                                                          |                                                                                                                                                                                        |
| 1     | G2TR-063<br>75 µg/<br>implant  | Untreated<br>control | 16 (4 or<br>7-8<br>samples<br>per time<br>point) | Day 7 (n=4),<br>Day 28 (n=4),<br>Day 180 (n=4),<br>& Day 211±7<br>(n=4)  | Aqueous humor (OD only) for<br>analysis (Collection at sacrifice only<br>on Day 7; tap on Days 28 and 180<br>followed by sacrifice the next day;<br>tap without sacrifice on Day 70±5) |
| 2     | G2TR-125<br>75 µg /<br>implant | Untreated<br>control | 16 (4 or<br>7-8<br>samples<br>per time<br>point) | Day 7 (n=4),<br>Day 28 (n=5#),<br>Day 180 (n=3),<br>& Day 211±7<br>(n=4) | Both eyes for possible future<br>analysis Implants collected from eye<br>Iris/ciliary body                                                                                             |

OD = right eye; OS = left eye

# N=4 animals were sacrificed and tissues collected on Day 28; additional N=1 animal sacrificed and tissues (terminal collection only, no aqueous humor survival tap) collected on Day 26 due to hind foot self-injury.

## Results

Mean AH and ICB TFA concentrations were generally steady throughout the study with a gradual decrease towards the end of the study at Day 211. Slightly lower values were observed for the G2-TR-125 (b) (4) compared to the G1-TR-063 (b) (4) implant. AH and ICB TFA levels were observed at all time points indicating no significant burst release of the drug by the implants between Days 8 and 211. Mean TFA concentrations for the G2-TR-063 implant ranged from 1.49-15.4 ng/mL in AH, and from 4.03-38.7 ng/g in ICB. Mean TFA concentrations for the G2-TR-125 implants ranged from 0.96-11 ng/mL in AH, and from 5.87- 40.9 ng/g in ICB. TFA levels were overall evenly maintained for both types of implants at all times except at Days 179-180 were higher numbers for several measurement in AH and ICB were obtained for both implants. The significance of this finding is unknown though. TFA levels were within the target therapeutic concentration of (b) (4) and were maintained for up to 211 days (Table 7).

Table 7: Travoprost Free Acid Concentrations in Aqueous Humor and Iris Ciliary Body in the 7-Month Pharmacokinetic Study in NZW Rabbits

| Group         | Study Day      | Mean $\pm$ SD Concentration |                          |
|---------------|----------------|-----------------------------|--------------------------|
|               |                | Aqueous Humor (ng/mL)       | Iris Ciliary Body (ng/g) |
| 1 – G2-TR-063 | 8              | 5.44 $\pm$ 3.39             | 8.98 $\pm$ 5.01          |
| 2 – G2-TR-125 | 8              | 2.49 $\pm$ 0.75             | 8.32 $\pm$ 5.13          |
| 1 – G2-TR-063 | 29 (tap)       | 3.04 $\pm$ 3.03             | NA                       |
|               | 30 (terminal)  | 2.98 $\pm$ 2.73             | 9.59 $\pm$ 4.68          |
| 2 – G2-TR-125 | 29 (tap)       | 3.29 $\pm$ 2.86             | NA                       |
|               | 30 (terminal)  | 2.55 $\pm$ 3.50             | 5.87 $\pm$ 1.50          |
| 1 – G2-TR-063 | 73 (tap)       | 2.20 $\pm$ 2.71             | NA                       |
| 2 – G2-TR-125 | 73 (tap)       | 4.34 $\pm$ 3.71             | NA                       |
| 1 – G2-TR-063 | 179 (tap)      | 12.7 $\pm$ 17.1             | NA                       |
|               | 180 (terminal) | 15.4 $\pm$ 17.1             | 38.7 $\pm$ 3.58          |
| 2 – G2-TR-125 | 179 (tap)      | 11.0 $\pm$ 24.6             | NA                       |
|               | 180 (terminal) | 2.32 $\pm$ 1.85             | 40.9 $\pm$ 19.2          |
| 1 – G2-TR-063 | 211 (terminal) | 1.49 $\pm$ 0.94             | 4.03 $\pm$ 0.99          |
| 2 – G2-TR-125 | 211 (terminal) | 0.96 $\pm$ 0.99             | 2.75 $\pm$ 0.98          |

SD = standard deviation; NA = not applicable

(Copied from 16C95Q2 on p 19)

## METABOLISM/EXCRETION

No additional metabolism or excretion studies were conducted.

*This reviewer's comment: The metabolism and excretion of travoprost and its hydrolysis product, TFA, after ocular administration have been well characterized for the LD.*

## 5.2 Toxicokinetics

### *Study conducted by the Sponsor*

Toxicokinetic (TK) assessment was conducted in a GLP 6-month ocular and systemic toxicity study in minipigs (Study CB14-5048-P-TX).

Studies reviewed by Dr. McDougal in IND 120995<sup>4</sup>

**CB14-5048-P-TX: 6-Month Ocular and Systemic Toxicity in Minipigs**  
Methods

One or two G2-TR-125 Travoprost Intraocular Implants, i.e., 75 or 150 µg travoprost, were inserted into the anterior chamber angle of the right eye of Yucatan minipigs. Left eyes were implanted with an empty control implant or untreated. Animals were terminated at Day 90 or Day 180 (2/sex/group/timepoint). Plasma was collected for toxicokinetics at pre-dose and days 7, 30, 90 and 180.

## Results

Plasma TFA concentrations were below the LLOQ (0.2 ng/mL) at all timepoints for all groups.

# 6 General Toxicology

## 6.1 Single-Dose Toxicity

The Sponsor conducted a 6-month safety and pharmacokinetic study (Study 14C94Q1R1G62) in New Zealand White (NZW) rabbits, and a 6-month ocular and systemic toxicity study in Yucatan minipigs (Study CB14-5048-P-TX), both according to GLP standards. Safety endpoints were also incorporated in non-GLP studies such as a 28-Day Ocular Pharmacokinetic and Tolerability Study in Rabbits (Study 12C94Q3R2) and a 12-Month Ocular Pharmacokinetic/ Pharmacodynamic and Tolerability Study in Cynomolgus Monkeys (Report 08-104).

These studies were reviewed by Dr. McDougal with IND 120995<sup>4</sup> submission.

*This reviewer's comment: The Sponsor did not per se directly compare Travatan® to the implant in any of their studies. The studies narrated below were reviewed in the PK/ADME/TK section of this review for what pertained to the exposure data. In this section, the tolerability/toxicity of the implant was explored. Key results were extracted from the PT review of Dr. McDougal<sup>4</sup>.*

### 12C94Q3R2: 28-Day Ocular Pharmacokinetic and Tolerability Study in Rabbits

#### Methods

In this non GLP pharmacokinetic study, two G2-TR-125 Travoprost Intraocular Implants (b) (4) containing 75 µg (corrected from (b) (4)) per implant, were implanted into the right eye anterior chamber angle of male NZW rabbits. The Animals were sacrificed on Days 14 and 28 (6/timepoint) and blood, and ocular tissues were collected to assess tissues and fluids exposure to TFA. Other parameters evaluated in all

animals on Days 7, 14, and 28, were clinical observation, ophthalmic examination, pupillometry, and histopathology on Day 28.

#### Key findings

- Grade 1 corneal cloudiness and grade 1 pannus were observed (at the injection site) at all post-surgery time points (D7-D28) in all implant-injected eyes
- Mild irritation (grade 1 conjunctival congestion, grade 1 iris vessel injection) were observed in most or all eyes at all post-surgery time points (D7-D28)
- 3/24 implants moved or bent. Based at least partially on the results of this study, the titanium implant was redesigned prior to use in humans
- Corneal tears devoid of inflammation in all implanted eyes at the location of the implant
- Synechia in one eye out of six, i.e., adherence of the iris to the cornea, with a focal area of inflammation at the junction of the iris lying on the caudal limiting membrane of the cornea (Descemet's membrane)
- Healing surgical scars

*This reviewer's comment: Dr. McDougal found the lack of corneal cloudiness resolution at Day 28 and the presence of a synechia in one eye out of six concerning. Since two few animals were used in this non-GLP study to make a proper assessment, this reviewer judged the findings could be related to the procedure rather than the implant unless they duplicated in an adequately performed GLP study.*

#### *14C94Q1R1G62: Ocular distribution and safety of the Sponsor's test article after implantation in the eyes of male and female New Zealand White rabbits*

##### Methods

The ocular toxicity of Travoprost Intraocular Implant after a single intracameral injection was assessed as part of a 6-month ocular pharmacokinetic GLP study conducted in New Zealand White rabbits. One G2-TR-125 Travoprost Intraocular Implant (b) (4) containing 75 µg (corrected from (b) (4)) travoprost was implanted in the anterior angle chamber of the right eye of each animal and the left eye was left untreated. The animals were terminated at Days 7, 28, 90 and 181 (3 animals/sex/timepoint). In life parameters evaluated were clinical and gross ocular examinations (daily), ophthalmology with a slit-lamp biomicroscope and an indirect ophthalmoscope at baseline, and at Days 7, 13, 21, 28, 61, 90, 119, 153 and 181, scored using a modified McDonald-Shadduck system (iris pigmentation was also assessed), and pupillometry on Days 1, 7, 14, 21, 28, 61, 90, 92, 119, 162, and 181.

## Study design

| Group | N    |        | Treatment (OD)                   | Treatment (OS)    | Dose (µg/implant) | Termination time point | Matrices collected                                                                                                             |
|-------|------|--------|----------------------------------|-------------------|-------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------|
|       | Male | Female |                                  |                   |                   |                        |                                                                                                                                |
| 1     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 7                  | Blood (for plasma)                                                                                                             |
| 2     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 28                 | Treated eye (OD) only: aqueous humor, vitreous humor, lens, iris/ciliary body, retina, choroid, sclera, conjunctiva and cornea |
| 3     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 90                 |                                                                                                                                |
| 4     | 3    | 3      | Intracameral Ocular Implantation | Untreated Control | 75                | Day 181                |                                                                                                                                |

## Key findings

The implantation procedure caused transient ocular irritation (congestion, pannus, iris hyperemia, and corneal loss of transparency). These effects resolved by Day 21 or Day 28. There was no test article related ocular side effects in the limit of the parameters evaluated in this study. As no histopathology took place, no definitive ocular and systemic NOAELs could be established.

*This reviewer's comment: There were too few animals at necropsy per time points (the Agency recommends a minimum of 4 non rodents per gender per dose group at terminal necropsy in a GLP toxicity study) and there was no recovery period considering that each implant may release travoprost for over 12 months. However, since there were no implant-related findings for up to 6 months and travoprost ocular effects are quite well known, allied with the minipigs findings (see below), this reviewer found the results in the rabbit acceptable albeit suboptimal due to study design issues. The ocular data in the rabbit represented a 1-fold ocular clinical safety margin with the dose in the implant.*

*CB14-5048-P-TX: 6-Month Ocular and Systemic Toxicity in in Yucatan Miniature Swine*  
Methods

In this GLP study, one or two G2-TR-125 Travoprost Intraocular Implants (total of 75 µg (corrected from (b) (4)) or 150 µg travoprost, respectively) were injected into the anterior chamber angle of the right eye (intracamerally). Left eyes were implanted with an empty control implant or left untreated. Animals were terminated at Day 90 or Day 180 (2/sex/group/timepoint). Parameters evaluated were mortality/morbidity (daily), clinical and gross ocular observations (daily), body weights (weekly), food consumption (daily), ophthalmology (at pre-dose, and post-dose at Days 7, 60, 84, and 175; grading of lesions by the McDonald- Shadduck scoring system), intraocular pressure (IOP) (at pre-dose, and post-dose at Days 7, 28, 60, 84 and 175), electroretinography (ERG) (at pre-dose, and post-dose at Days 7, 28, 84 and 175), electrocardiography (ECG) (at pre-dose, and post-dose at Days 30, 90 and 180), clinical pathology analysis ( hematology, coagulation and clinical chemistry at pre-dose, and post-dose at Days 7, 30, 60, 90 and 180), macroscopic observations, organs weights, and microscopic examination of the eyes, ocular adnexa and systemic tissues.

## Study design

| Group | Animal No.<br>(male/<br>female) | Necropsy<br>Day | Day 0                                                     |                                                      | Days 0 - 180                                                                                                                                                                                                                                                                                                                                          |
|-------|---------------------------------|-----------------|-----------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|       |                                 |                 | OD<br>(Travoprost)                                        | OS<br>(Empty) <sup>#</sup>                           |                                                                                                                                                                                                                                                                                                                                                       |
| 1     | M: 101-102<br>F: 151-152        | 90              | Single<br>Travoprost<br>Intraocular<br>Implant<br>(75 µg) | None                                                 | Clinical observations: daily<br>Clinical ophthalmic observations:<br>daily<br>Body weights: pre-dose and once<br>weekly thereafter.                                                                                                                                                                                                                   |
| 2     | M: 201-202<br>F: 251-252        |                 | Two Travoprost<br>Intraocular<br>Implants<br>(2 x 75 µg)  | Single<br>Control<br>Empty<br>Intraocular<br>Implant |                                                                                                                                                                                                                                                                                                                                                       |
| 3*    | M: 301-302/<br>F: 351-352       | 180             | Single<br>Travoprost<br>Intraocular<br>Implant<br>(75 µg) | None                                                 | Ocular examinations (by<br>ophthalmologist) and tonometry:<br>pre-dose and days 7±1, 28±1, 62,<br>84±1 and 176<br>Blood for TK analysis: pre-dose<br>and days 7, 30, 90 and 180*<br>Blood for clinical pathology: pre-<br>dose and days 7, 30, 60, 90, 180<br>ECG: pre-dose and days 32, 89, and<br>180<br>ERG: pre dose and days 7±1, 28, 84,<br>176 |
| 4*    | M: 401-402/<br>F: 451-452       |                 | Two Travoprost<br>Intraocular<br>Implants<br>(2 x 75 µg)  | Single<br>Control<br>Empty<br>Intraocular<br>Implant |                                                                                                                                                                                                                                                                                                                                                       |

\* Groups 3 and 4 only. <sup>#</sup> Control article is an unloaded titanium implant. OD – Right eye. OS – Left eye.

Terminal procedures (day 90 to 180) in all groups included 1) body weight, 2) blood for clinical pathology and TK, 3) sacrifice and necropsy for collection of complete tissue list, and 4) histopathology on eyes.

M = Male. F = Females

## Key findings

No treatment-related toxicity was observed, and the ocular NOAEL was the high-dose tested (i.e., 2 implants/OD). This represented a 2-fold ocular clinical safety margin with the dose in the implant and a 1.3-fold systemic clinical safety margin (calculated for a 60 kg human and a 40 kg minipig) based on a 6-month, continuous, sustained-release of travoprost at the same rate/day.

*This reviewer's comment: There were too few animals at necropsy per time points (the Agency recommends a minimum of 4 non rodents per gender per dose group at terminal necropsy in a GLP toxicity study) and there was no recovery period considering that each implant may release travoprost for over 12 months. However, since there were no implant-related findings for up to 6 months, travoprost ocular effects are quite well known, and the results were consistent with the GLP rabbit study, this reviewer found the study results acceptable albeit suboptimal due to study design issues.*

*Report 08-104: 12-Month Ocular Pharmacokinetic/ Pharmacodynamic and Tolerability Study in Cynomolgus Monkeys*

Methods

In this proof of concept, non GLP study, one G2-TR-036 implant ( [REDACTED] (b) (4) ), representative of the Travoprost Intraocular Implant [REDACTED] (b) (4) to accommodate the smaller ocular anatomy of the cynomolgus monkey) was implanted in the anterior chamber angle of 1 eye of 4 female cynomolgus monkeys that were IOP-responsive to Travatan (travoprost ophthalmic solution, 0.004%). Animals were terminated at 12 months. Parameters evaluated were clinical observations, ophthalmic examinations, IOP (weekly and then at 2, 6, 7, and 9 months), and anterior segment imaging with an optical coherence tomograph (AS-OCT).

Key findings

Dr. McDougal reported some dark streaking of the iris (pigmentation), which corresponded with the implantation path in 3/4 monkeys, that persisted throughout the study period of 15 months. The data was not useful for evaluating safety, due to inadequate study design and reporting (non GLP study). In addition, the titanium implant design was different from what was used in the Phase 1 trial, and from the final product. This reviewer agrees.

SAFETY BRIDGE WITH TRAVATAN®

*Systemic*

The systemic exposures with the implant in all preclinical studies were below the LLOQ of 200 pg/mL with no report of systemic toxicity in the GLP study in the minipig (all other studies did not include in their designs the histopathology of either the eyes and adnexa and/or the systemic tissues).

The Sponsor reported that in the clinic, the systemic exposure following the implantation of one Travoprost Intraocular Implant into one eye of patients was below the LLOQ of 10 pg/mL (Module 2.7.2). Travatan® PI<sup>2</sup> indicated travoprost, absorbed through the cornea and hydrolyzed to TFA had plasma concentrations of TFA below 10 pg/mL (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma C<sub>max</sub> was 18 ± 7 pg/mL (ranged 10 to 52 pg/mL) and was reached within 30 minutes. From these studies, travoprost was estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady state was reached early and that there was no significant accumulation. As a corollary, the Sponsor

believed they have established a systemic safety bridge with Travatan® since the systemic exposure was lower with their product than with Travatan®.

*This reviewer's comment: The LLOQ was too high in the pig study to be able to appreciate the true systemic exposure in the animal study and establish the clinical systemic safety margin based on exposure rather than on dose which was only 1.36X according to the pig data. This does not adequately support the clinical dose as the safety margin is less than 10X. However, a higher dose in the pig could not be administered.*

#### Ocular

As no direct comparison study with Travatan® in any of the animal studies occurred, in his review, Dr. McDougal compared the ocular exposure with G2TR-125 to the LD using an online published redacted version of the pharmacology and toxicology review of NDA 21-257<sup>11</sup> by Dr. Zhou Chen at FDA.

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<sup>11</sup>[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2001/21257\\_Travatan.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21257_Travatan.cfm)

Dr. McDougal reported that in a single-dose topical ocular distribution study in rabbits (Study # 019:38570:0598 in NDA 21247), the animals received 30 µL of 0.004% Travatan® in one eye (equivalent to 1.2 µg of travoprost or 1.6% of the total dose in the G2TR-125 implant, 75 µg). Samples were collected from 4 rabbits/time point at 10 time points (up to 72 hours post-dose). In this study, the drug product distributed in descending order into cornea > conjunctiva > aqueous humor > iris/ciliary body > choroid > retina > lens > plasma > vitreous humor (Table 8). The aqueous humor C<sub>max</sub> was 21.8 ng/mL, and TFA was detected in the plasma with a C<sub>max</sub> of 0.078 ng/mL. Compared to the exposures achieved with the implant in the AH in the rabbit of 4.03 ng/mL, and 4.20 ng/mL, in Study 12C94Q3R2, and 14C94Q1R1G62, respectively, Dr. McDougal concluded “the data provided an adequate bridge for safety”. For ease of comparison with Table 8, Table 4 and Table 5 for the implant were reproduced underneath.

This data is for informational purposes only and does not imply reliance on PK from the previously conducted rabbit study for NDA 21247 to establish a scientific bridge to Travatan.

Table 8: Ocular distribution data for topical ocular travoprost (from the NDA 21257 PT review)

**Distribution of radioactivity in ocular tissues of rabbits treated with <sup>3</sup>H-AL-6221**

|                                        | Aqueous humor | Choroid | Conjunctiva | Cornea | Iris-ciliary body | Lens  | Retina | Vitreous humor | plasma |
|----------------------------------------|---------------|---------|-------------|--------|-------------------|-------|--------|----------------|--------|
| <b>C<sub>max</sub> (ng-eq/g)</b>       | 21.8          | 2.05    | 105         | 327    | 15.0              | 0.135 | 0.153  | 0.025          | 0.078  |
| <b>T<sub>max</sub> (hr)</b>            | 2.0           | 1.0     | 0.5         | 0.5    | 1.0               | 2.0   | 1.0    | 1.0            | 0.5    |
| <b>T<sub>1/2</sub> (hr)</b>            | 1.5           | 1.1     | 1.4         | 13.8   | 1.5               | 28.6  | 0.5    | 0.4            | 2.6    |
| <b>AUC<sub>0-24</sub> (ng-eq hr/g)</b> | 27.2          | 4.0     | 168         | 766    | 49.3              | 3.41  | 0.266  | 0.055          | 0.175  |

(Copied from Dr. McDougal's review of IND120995<sup>4</sup> on p 50)

For comparison:

[Table 4: Travoprost Free Acid Concentrations in Ocular Tissues from the Non-GLP 28-Day Ocular Pharmacokinetic Study in Rabbits (Study 12C94Q3R2)]

| Tissue                   | Average Concentration (SD)<br>ng/mL or ng/g* |              |
|--------------------------|----------------------------------------------|--------------|
|                          | Day 14                                       | Day 28       |
| <b>Aqueous humor**</b>   | 4.78 (2.79)                                  | 5.03 (3.47)  |
| <b>Iris/Ciliary body</b> | 27.6 (26.1)                                  | 16.8(4.28)   |
| <b>Vitreous humor</b>    | BLOQ                                         | BLOQ         |
| <b>Retina</b>            | 2.23 (NC)                                    | BLOQ         |
| <b>Sclera</b>            | 5.20 (2.05)                                  | 4.57 (1.97)  |
| <b>Cornea</b>            | 17.1 (21.7)                                  | 11.0 (2.48)  |
| <b>Lens</b>              | BLOQ                                         | BLOQ         |
| <b>Choroid</b>           | BLOQ                                         | 2.90 (0.441) |

BLOQ = Below Limit of Quantitation (&lt; 0.2 ng/mL for AH and VH, &lt; 2 ng/g for other tissues)

SD = Standard deviation, NC= not calculated, due to limited data

\* Values are in ng/mL for aqueous and vitreous humor and ng/g for all other tissues

\*\* The pilot study animal value was used for the AH result for 14-day results (n = 7); all other tissue values are n = 6

(Copied from the PT review of IND 120995<sup>4</sup> on p 42)

Table 5: Travoprost Free Acid Concentrations in Ocular Tissue in the GLP 6-Month Ocular Toxicity and Pharmacokinetic Study in NZW Rabbit (Study 14C94Q1R1G62)

| Tissue                   | Average (SD) Concentration [ng/mL (humors) or ng/g (tissues)] |             |             |             |
|--------------------------|---------------------------------------------------------------|-------------|-------------|-------------|
|                          | Day 7                                                         | Day 28      | Day 90      | Day 180     |
| <b>Aqueous humor</b>     | 17.58 (7.92)                                                  | 4.20 (7.18) | 1.96 (1.15) | 4.33 (2.22) |
| <b>Vitreous humor</b>    | BLOQ                                                          | 0.239 (NC)  | 0.238 (NC)  | BLOQ        |
| <b>Retina</b>            | BLOQ                                                          | BLOQ        | BLOQ        | BLOQ        |
| <b>Sclera</b>            | 3.89 (1.30)                                                   | 2.68 (0.37) | 3.34 (1.22) | 2.89 (NC)   |
| <b>Cornea</b>            | 37.80 (20.79)                                                 | 9.83 (9.02) | 3.99 (2.68) | 8.44 (9.66) |
| <b>Lens</b>              | BLOQ                                                          | BLOQ        | BLOQ        | BLOQ        |
| <b>Choroid</b>           | BLOQ                                                          | BLOQ        | BLOQ        | BLOQ        |
| <b>Iris/Ciliary body</b> | 20.93 (6.55)                                                  | 6.95 (3.29) | 9.27 (2.49) | 8.60 (3.92) |
| <b>Conjunctiva</b>       | 3.86 (1.11)                                                   | 4.06 (2.29) | 5.88 (4.48) | 3.19 (0.23) |

BLOQ = Below Limit of Quantitation

NC = Not calculated

SD = Standard deviation

(Copied from the PT review of IND 120995<sup>4</sup> on p 35)]

## 6.2 Repeat-Dose Toxicity

Not applicable.

*This reviewer's comment: The duration of travoprost release by the implant is at least 6 months and no repeat dose toxicity study was needed. In general, the Division recommends ocular toxicity studies of 6 months in two pharmacologically active species for product registration, unless systemic toxicity was observed in shorter studies, then a longer duration may be needed.*

## 7 Genetic Toxicology

For this Section, the Sponsor relied on the information from their LD Travatan® which this reviewer found to be acceptable.

From Travatan® PI, 2011<sup>2</sup>

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

## 8 Carcinogenicity

For this Section, the Sponsor relied on the information from their LD Travatan® which this reviewer found to be acceptable except that, for the calculation of the safety margins with their clinical dose, they have used data they do not own (an IR was sent to the Sponsor on May 02, 2023, to which they responded on June 10, 2023).

From Travatan® PI, 2011<sup>2</sup>

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day travoprost did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study.

Referring to the data in the preclinical review of NDA 021257 for Travatan®, the Sponsor added that the highest dose of 100 µg/kg/day was 1,840-times the human systemic exposure (calculated based on estimated 10 pg/mL TFA plasma exposure from Travoprost Intraocular Implant in humans, using the LLOQ of 10 pg/mL, and plasma C<sub>max</sub> of 18.4 ng/mL in rat PK subcutaneous study at the 100 µg/kg dose [Travatan NDA 021257, 2001]).

*This reviewer's comment: The Sponsor may not use the proprietary data in NDA 021257 that they do not own.*

## 9 Reproductive and Developmental Toxicology

For this Section, the Sponsor relied on the information from their LD Travatan® which this reviewer found to be acceptable except for the calculation of the safety margins with their clinical dose since the Sponsor may not use the proprietary data in NDA 021257 that they

do not own (an IR was sent to the Sponsor on May 02, 2023, to which they responded on June 10, 2023).

## 9.1 Fertility and Early Embryonic Development

From Travatan® PI, 2011<sup>2</sup>

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

Referring to the data in the preclinical review of NDA 021257 for Travatan®, the Sponsor added that the dose of 10 µg/kg/day, was 1,840-times the human systemic exposure, (calculated based on an estimated plasma TFA of 10 pg/mL in humans with a Travoprost Intraocular Implant and a plasma C<sub>max</sub> of 18.4 ng/mL in rat at a subcutaneous dose of 100 µg/kg [Travatan NDA 021257, 2001]) and the dose of at 3 µg/kg/day was 179-times the human systemic exposure (calculated based on estimated plasma TFA of 10 pg/mL in humans with a Travoprost Intraocular Implant and a plasma C<sub>max</sub> of 1.79 ng/mL in rat at a subcutaneous dose 10 µg/kg [Travatan NDA 021257, 2001]).

*This reviewer's comment: The Sponsor may not use the proprietary data in NDA 021257 that they do not own.*

## 9.2 Embryonic Fetal Development

From Travatan® PI, 2011<sup>2</sup>

Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal

viability in rats at IV doses >3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses >0.3 mcg/kg/day (7.5 times the MRHOD).

### 9.3 Prenatal and Postnatal Development

From Travatan® PI, 2011<sup>2</sup>

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of  $\geq 0.12$  mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

Referring to the data in the preclinical review of NDA 021257 for Travatan®, the Sponsor added that the dose of 0.12 mcg/kg/day was 2-times the human systemic exposure (calculated based on an estimated plasma TFA of 10 pg/mL in humans with a Travoprost Intraocular Implant and an extrapolated plasma  $C_{max}$  of 0.0215 ng/mL in rat at a dose of 10  $\mu$ g/kg [Travatan NDA 021257, 2001]).

*This reviewer's comment: The Sponsor may not use the proprietary data in NDA 021257 that they do not own.*

*An IR was sent to the Sponsor on May 02, 2023, with the following comments:*

- 1. Provide human dose multiples for embryofetal toxicity data in Section 8 of labeling. Also submit all calculations and sources of data values (literature, study number, etc.) to the NDA.*
  - a. Estimation of exposure should originate from pharmacokinetic/ toxicokinetic data in the reproductive and developmental toxicity studies with travoprost, rather than from data derived from general toxicology studies.*
- 2. Clinical safety margins should be based on AUC rather than  $C_{max}$  values derived from the peer-reviewed literature.*
- 3. Proprietary data from a listed drug that is not found in product labeling may not be used for calculation of multiples for your studies.*

*The Sponsor provided a response on 06-10-2023 in SDN 0010 (see labeling review).*

## 10 Special Toxicology Studies

No special toxicology studies were performed either with Travatan® or the Travoprost Intraocular Implant.

## 11 Integrated Summary and Safety Evaluation

The Sponsor is proposing to use Travoprost Intraocular Implant, 75 µg for the treatment of increased IOP associated with OAG or OH.

This NDA 505(b)(2) submission is relying on parts of the non-clinical labelling information for their LD Travatan®, i.e., for genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

The ocular and systemic toxicity of the implant was studied in two 6-month ocular GLP toxicity studies in the rabbit and the minipig. The implant was well tolerated in both studies. However, there was a <10X systemic safety margin established between the clinical dose and the doses used in the minipig study (Table 9B below).

Based on the good tolerance of the implants in both the rabbit and the minipig for up to 6 months post-injection, end of the studies, and based on the well-known ocular toxicity of travoprost the ocular safety was found to be acceptable despite the low clinical ocular safety margins with the animal NOAELs (Table 9A).

To establish a systemic safety bridge and be able to rely on some of the information contained in the label for Travatan®, the Sponsor showed that the systemic exposure achieved in patients with the implant was lower than with Travatan® applied topically to both eyes either with one insert in one eye or, one insert in each eye. Therefore, the clinical pharmacology team concluded that a bridge with Travatan® was justified.

Table 9: Clinical Safety Margins (created by this reviewer)

A

**Ocular Safety Margins Based on Ocular NOAELs in the GLP Toxicity Studies**

| Species | NOAEL<br>mg/dose                                   | Total Dose<br>(µg/eye) | Margins of Exposure*<br>Based on Total Dose          |
|---------|----------------------------------------------------|------------------------|------------------------------------------------------|
|         |                                                    |                        | MRHD = 75 µg/eye/single intracameral<br>implant once |
| Rabbit  | 75 µg/eye/ intracameral<br>implant once in one eye | 75                     | 1X*                                                  |
| Minipig | 150 µg/eye/intracameral<br>implant once in one eye | 150                    | 2X*                                                  |

NOAEL = no-observed-adverse-effect level

MRHD = maximum recommended human dose

\*Calculated based on a 6-month continuous elution of travoprost by the implant at the same rate/day in the animal and in man

**B****Systemic Safety Margins Based on Systemic NOAELs in the GLP Toxicity Studies**

| Nonclinical                                        |                     |                |                        | Clinical Safety Margins*<br>(Based on Dose in mg/m <sup>2</sup> equivalent) |
|----------------------------------------------------|---------------------|----------------|------------------------|-----------------------------------------------------------------------------|
| Species/ Duration                                  | NOAEL<br>(µg/kg)    | HED<br>(µg/kg) | C <sub>max</sub> /AUC  | MRHD <sup>(1)</sup> = 2.5 µg/kg<br>based on 1 implant <i>per</i><br>eye/OU  |
| Rabbit/intracameral<br>implant once in one<br>eye  | NA                  | NA             | Below LLOQ (0.2 ng/mL) | NA                                                                          |
| Minipig/intracameral<br>implant once in one<br>eye | 3.75 <sup>(2)</sup> | 3.41           | Below LLOQ (0.2 ng/mL) | 1.36X                                                                       |

NOAEL = no-observed-adverse-effect level

LLOQ = Lower Limit of Quantitation

C<sub>max</sub> = maximal concentration<sup>(1)</sup> Calculation based on a 60 kg adult human<sup>(2)</sup> Calculation based on a 40 kg minipig

HED = human equivalent dose

AUC = area under the concentration-time curve

MRHD = maximum recommended human dose

NA = Not applicable

\*Calculated based on a 6-month continuous elution of travoprost by the implant at the same rate/day in the animal and in man

## 12 Appendix/Attachments

Non applicable.

### References

Denis P, Covert D, Realini A. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clin Ophthalmol 2007;1(1):11-24.

Faulkner RD, Sharif NA, Sall K, et al. Aqueous humor concentrations of bimatoprost free acid, bimatoprost and travoprost free acid in cataract surgical patients administered multiple topical ocular doses of Lumigan or Travatan. J Ocul Pharmacol Ther. 2010;26(2):147-56.

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/s/  
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MURIEL J SAULNIER  
11/20/2023 11:39:38 AM

KIMBERLY P HATFIELD  
11/20/2023 01:19:22 PM  
I concur with the review and recommendations of Dr. Saulnier.