

ENVISIA THERAPEUTICS INC.

Clinical Study Protocol ENV515-01 Incorporating Amendment 10

Project: ENV515

Compound Number/Name: ENV515-1, ENV515-3, and ENV515-3-2 (travoprost) Intracameral Implants

Protocol Number: ENV515-01

Protocol Title: A Multi-Center, Three-Stage, Open-Label, Prospective, Active-Comparator-Controlled Phase 2a Study of ENV515 (travoprost) Intracameral Implant in Patients with Bilateral Ocular Hypertension or Early Primary Open Angle Glaucoma

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Issue Date:

Original Protocol:	October 31, 2014
Amendment 01:	January 20, 2015
Amendment 02:	June 2, 2015
Amendment 03:	October 14, 2015
Amendment 04:	July 28, 2016
Amendment 05:	November 10, 2016
Amendment 06:	December 29, 2016
Amendment 07:	April 13, 2017
Amendment 08:	August 23, 2017
Amendment 09:	November 30, 2017
Amendment 10:	February 19, 2018

IND No: 119347

This study will be conducted in accordance with the protocol and in compliance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH) guidelines, and any other applicable regulatory requirements. Envisia will also continue to support the principles of the Declaration of Helsinki.

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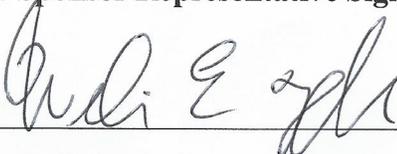
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PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Title: A Multi-Center, Three-Stage, Open-Label, Prospective, Active-Comparator-Controlled Phase 2a Study of ENV515 (travoprost) Intracameral Implant in Patients with Bilateral Ocular Hypertension or Early Primary Open Angle Glaucoma

Protocol Number: ENV515-01 Amendment 10

Authorized Sponsor Representative Signature

Signature:  Date: February 19th, 2018

Name: William Yelle

Title: Board Chairman

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title: A Multi-Center, Three-Stage, Open-Label, Prospective, Active-Comparator-Controlled Phase 2a Study of ENV515 (travoprost) Intracameral Implant in Patients with Bilateral Ocular Hypertension or Early Primary Open Angle Glaucoma

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I have reviewed and understand the ENV515-01 protocol and the most current Investigator’s Brochure. I will administer the protocol in accordance with ICH, FDA, and local regulations and guidelines. I will keep the information provided to me within this protocol and by Envisia Therapeutics staff, their representatives, and designees confidential.

Principal Investigator’s Signature

Date

Name (print): _____

Clinical Site/Institution: _____

Address: _____

ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 1

Cohort 1 Protocol Synopsis

Investigational Product: ENV515-1 and ENV515-3 (Travoprost) Intracameral Implant

Phase: 2a

Study Objective:

- Evaluate the safety, tolerability, efficacy, aqueous humor PK, systemic exposure, and remaining travoprost in ENV515 implants following a single dose of 4 dose levels of ENV515 (travoprost) intracameral implants/eye in patients with bilateral ocular hypertension or primary open-angle glaucoma
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Clinical Hypotheses:

- A single dose of ENV515 (travoprost) Intracameral Implant is comparable to TRAVATAN Z ophthalmic solution dosed once daily in the control of IOP over 25 days in patients with bilateral ocular hypertension or primary open-angle glaucoma
 - ENV515 (travoprost) Intracameral Implant has an acceptable safety profile
-

Study Design:

Structure: Cohort 1, the first-time-in-human Phase 2a clinical study conducted as a multicenter, randomized, open-label, parallel-group, dose-ranging, fellow-eye active-comparator-controlled, 28-day Phase 2a trial of 4 dose levels of ENV515 (travoprost) Intracameral Implant. Glaucoma patients scheduled for cataract removal will be dosed unilaterally in the study eye (pre-surgical eye) with ENV515 4 weeks prior to the cataract surgery and the implants will be retrieved during the cataract surgery.

Duration of Patient Participation: Approximately 10 to 12 weeks including up to a 42-day washout period, implantation/treatment administration day, 25 day primary efficacy and safety evaluation period post initial dose of ENV515 in the study eye, implant removal during cataract surgery on Day 28, and a safety follow-up for up to 2 weeks.

Study Treatment Investigational Product: ENV515 (travoprost) Intracameral Implant administered into the study eye as a single, unilateral dose via intracameral injection on Day 1

Reference Product: TRAVATAN Z administered into the non-study eye

Dosage/Dose Regimen/Treatment Groups:

- 4 dose levels of ENV515 (travoprost) Intracameral Implant achieved via the following numbers and sizes of implants: 28.2 µg (2 ENV515-3 implants), 42.3 µg (3 ENV515-3 implants), 42.5 µg (1 ENV515-1 implant), and 85.0 µg (2 ENV515-1 implants).
- Control Group: TRAVATAN Z ophthalmic solution administered QD daily in the non-study, fellow eye

Rescue Therapy: Both the study and non-study eyes may be treated at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

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Randomization/Stratification: To minimize bias, patients were assigned to 1 of the 4 dose levels of ENV515 within each investigative site. The non-study eye received TRAVATAN Z.

Visit Schedule: Visit schedule encompasses Screening Visit 1 (Day -35 to -28) followed by 4-week IOP-lowering medication washout period with up to 2-week additional extension to allow full washout, Baseline Visit 2 (Day -7 to -1), Randomization/ Treatment Visit 3 (Day 1), Treatment Visit 4 (Day 3 ± 1 day), Treatment Visit 5 (Day 7 ± 1 day), Treatment Visit 6 (Day 14 ± 1 day), Treatment Visit 7 (Day 21 ± 1 day), Treatment Visit 8 (Day 25 ± 1 day), Surgery Visit 9 (Day 28 ± 1 day), Follow-up Visit 10 (Day 33 to 38 ± 1 day), and Follow-up Visit 11 (Day 42 to 49 ± 1 day) for a total of 11 visits.

Study Population Characteristics:

Number of Patients: Following successful screening, approximately 20 patients were enrolled into the study within the United States.

Condition/Disease: The study population consisted of patients with a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma who were currently being treated with a topical prostaglandin analogue (PGA) in both eyes and who were scheduled for cataract surgery in their study eye.

Inclusion Criteria:

1. Provide written informed consent prior to study procedures.
2. Are between 18 and 85 years of age.
3. Have a willingness to comply with the investigator's instructions, attend study visits, and stop prior eye medications to treat glaucoma and/or ocular hypertension.
4. If female, patient must be non-pregnant and non-lactating, and those of childbearing potential must be using an acceptable method of birth control (i.e., an intrauterine contraceptive device with a failure rate of <1%, hormonal contraceptives, or a barrier method). If a female patient is abstinent, she must agree to use one of the acceptable methods if she becomes sexually active.
5. Have a diagnosis of bilateral ocular hypertension or mild to moderate primary open-angle glaucoma and have open normal appearing anterior chamber angles (Shaffer classification Grade 3 or 4, angle of approach 20° or larger).
6. Are currently treated with topical PGA for ocular hypertension.
7. At the Baseline Visit after washout (Visit 2), have IOP measurements that meet all of the following:
 - Have an IOP at 8:00 a.m. (±30 minutes) and at 10:00 a.m. (±30 minutes) between 22-34 mm Hg in both eyes with a ≤4 mm Hg difference between the eyes
 - Have an IOP at 4:00 p.m. (±30 minutes) between 19-34 mm Hg in both eyes with a ≤4 mm Hg difference between each eye
8. Have an IOP ≤34 mm Hg in each eye at all other time points prior to the Baseline Visit (Visit 2).

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9. At the Screening Visit (Visit 1), have an IOP in both eyes that is considered to be safe, so that clinical stability of vision and the optic nerve is likely throughout the trial.
10. Have endothelial cell counts of at least 2000 cells/mm² and normal endothelial cell morphology at the Screening Visit (Visit 1) as evaluated by central reading center.
11. Patient is a candidate for and has been scheduled for cataract extraction in a single eye within 60 days of Visit 1*.

* Following cataract removal, the patient may undergo additional procedures (e.g., iStent insertion).

Exclusion Criteria:

1. Are currently diagnosed with closed angle glaucoma, exfoliation syndrome or exfoliation glaucoma, and pigment dispersion or secondary glaucoma.
2. Have a history of glaucoma-related surgery (trabeculectomy, cryotherapy, laser iridotomy, etc.).
3. Have had intraocular conventional surgery, intraocular laser surgery, corneal refractive surgery or eyelids surgery within the past 3 months.
4. Are currently diagnosed with active infectious/noninfectious conjunctivitis, keratitis, uveitis, or moderate to severe blepharitis in either eye. (Chronic mild blepharitis or injection related to mild blepharitis, lid lag, mild dry eye or seasonal allergies are allowed.)
5. Are currently taking or have taken corticosteroids (oral, ocular, injectable, IV and/or topical) or used dermatology formulations of steroids in the vicinity of eyes in the 1 month prior to Visit 1 with the exception of inhaled, intranasal, or topical (dermal) steroids if on a stable dose; or have a history of chronic ocular corticosteroid (topical or intraocular) use within the past year.
6. Have a requirement for any ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Visit 2.
7. Have a history of recurrent corneal erosion syndrome, multiple corneal abrasions, or an abrasion that was slow to heal.
8. Have severe glaucoma with a mean defect (MD) worse than -8.0, central island of vision, or otherwise severe glaucoma that would not tolerate a possible short-term increase in intraocular pressure (IOP).
9. According to the investigator's best judgment, are at risk for progression of glaucoma, visual field (VF) or visual acuity (VA) worsening as a consequence of participation in the trial.
10. Have any abnormality preventing reliable applanation tonometry in either eye.
11. Have any corneal opacity or are uncooperative in such a way that restricts adequate examination of the ocular fundus or anterior chamber in either eye.
12. Are unwilling to discontinue use of contact lenses at least 2 days prior to Visit 2 for soft lenses and at least 7 days prior to Visit 2 for rigid gas permeable (RGP) lenses through completion of the study at Visit 11.
13. Have progressive retinal or optic nerve disease apart from glaucoma.
14. Have any clinically significant, serious, or severe medical or psychiatric condition.
15. Are, in the opinion of the investigator, unable or unwilling to comply with study procedures, including attending the scheduled study visits.

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16. Have a history, or a suspected history of drug or alcohol dependence in the preceding year.
17. Are unwilling to limit alcohol ingestion and smoking for the 8-hour period prior to and during study appointments after Visit 1.
18. Have received any investigational product within the past 30 days prior to Visit 1.
19. Have any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial such as travoprost or PLA excipients.
20. Have a history of insufficient response to PGA topical treatment, i.e., are PGA non-responders.
21. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same.
22. Have a central corneal thickness greater than 600 micrometers as determined by pachymetry at the Baseline Visit (Visit 2).
23. Had prior intraocular surgery or any ocular or systemic condition that may confound the study outcome per the investigator's recommendation.

Response Measures

Primary Efficacy Measure:

- Change from baseline in time-matched IOP measurements at Day 25 for study and non-study eye

Secondary Efficacy Measures:

- Change from baseline and percent change from baseline in time-matched IOP measurements for study eye and non-study at all other study time points and visits
- Difference in change from baseline and percent change from baseline in time-controlled IOP measurements between study eye and non-study eye at all study time points and visits
- Cumulative % of study and non-study eyes with at least 20, 25, and 30% reduction in IOP at all study time points and visits
- Cumulative % of patients with IOP <18 at all time points at each study visit
- Mean IOP at all visits all time points

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA
- Visual field

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- Physical examination
- Vital signs
- Non fasting clinical laboratory tests (chemistry and hematology)
- Serum or urine pregnancy tests for females of childbearing potential
- AEs

Pharmacokinetic Measures:

- Systemic exposure to travoprost via analysis of travoprost acid in plasma;
- Ocular exposure to travoprost via analysis of travoprost acid in aqueous humor.

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Table 1: Time and Events Schedule, Cohort 1

Procedure	Screening V1 Day -35 to -28	Baseline V2 -7 to -1 Days	Randomization/ Treatment V3 Day 1	Treatment V4 Day 3 +/- 1 day	Treatment V5 Day 7 +/- 1 day	Treatment V6 Day 14 +/- 1 day	Treatment V7 Day 21 +/- 1 day	Treatment V8 Day 25 +/- 1 day	Surgery V9 Day 28	Follow-up V10 Day 33-38	Follow-up V11 Day 42-49
Informed consent review	X										
Demographics/ medical & ocular history	X										
Concomitant medication query	X	X	X	X	X	X	X	X	X	X	X
Adverse events query	X	X	X	X	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X	X	X	X	X
Pupil measurement	X	X				X		X		X	
Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X	X
Corneal staining	X	X	X	X	X	X	X	X	X	X	X
IOP check (8:00 a.m.)	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X	X		X		X	X	X	X	X	
Pachymetry (contact)	X	X				X		X		X	
Specular microscopy (non-contact)	X ¹	X				X		X			X ¹
Visual field	X									X	
Anterior segment OCT	X	X		X		X		X		X	
IOP diurnal curve		X ²						X ²			
Dilated fundus exam	X	X				X		X		X	

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Procedure	Screening V1 Day -35 to -28	Baseline V2 -7 to -1 Days	Randomization/ Treatment V3 Day 1	Treatment V4 Day 3 +/- 1 day	Treatment V5 Day 7 +/- 1 day	Treatment V6 Day 14 +/- 1 day	Treatment V7 Day 21 +/- 1 day	Treatment V8 Day 25 +/- 1 day	Surgery V9 Day 28	Follow- up V10 Day 33- 38	Follow- up V11 Day 42- 49
Physical exam	X	X								X	
Vitals	X	X								X	
Lab tests	X	X ³				X ³				X ³	
Pregnancy test	X	X	X							X	
Study drug administration			X								
Cataract surgery									X		
Aqueous humor collection									X		
Implant recovery									X		
Dispense TRAVATAN Z			X								
Collect TRAVATAN Z								X			
Receive pre-surgical medications								X			
Dismiss patient, complete exit form											X

¹ Non-contact specular microscopy can be performed anytime during the site visit.

² IOP will be measured at 8 a.m., 10 a.m., and 4 p.m. for the diurnal curve endpoint.

³ Blood draws will be conducted prior to the daily administration of the TRAVATAN Z into the non-study eye. Samples collected as Visits 6 and 10 will additionally be used to determine the systemic exposure to travoprost as described in [Sections 15.1.7](#) and [1.6](#).

ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 2

Cohort 2 Protocol Synopsis

Investigational Product: ENV515-3 (Travoprost) Intracameral Implant

Phase: 2a

Study Objective:

- Evaluate the long-term safety, tolerability, efficacy, and systemic exposure to travoprost following a unilateral, single dose of two ENV515-3 (travoprost) intracameral implants in the study eye in patients with bilateral ocular hypertension or primary open-angle glaucoma
-

Clinical Hypotheses:

- A single dose of ENV515-3 (travoprost) Intracameral Implant is numerically comparable to timolol maleate 0.5% ophthalmic solution dosed twice daily in the control of IOP over 12 months in patients with bilateral ocular hypertension or primary open-angle glaucoma
 - ENV515-3 (travoprost) Intracameral Implant has an acceptable safety profile
-

Study Design:

Structure: The Cohort 2 phase of the Phase 2a clinical study is an up to 12-month, prospective, open-label, active-comparator-controlled, multi-center study of ENV515-3 (travoprost) Intracameral Implant. While the Cohort 1 enrolled glaucoma patients scheduled for cataract removal and the ENV515 implants were removed after 28 days during the cataract procedure, the Cohort 2 phase of the study will enroll glaucoma patients without the need for cataract surgery in order to study ENV515 over its entire duration of IOP-lowering efficacy, or up to 12 months after the first dose.

Duration of Patient Participation: Approximately a maximum of 14 months including up to a 49 day washout period, implantation/treatment administration day, 3 month primary efficacy and safety evaluation period post initial dose of ENV515 in the study eye, and a follow-up for 9 months after the 3 month primary efficacy and safety evaluation period

Study Treatment Investigational Product: ENV515-3 (travoprost) Intracameral Implant

Reference Product: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Dosage/Dose Regimen/Treatment Groups:

ENV515-3 Group: Two ENV515-3 (travoprost) implants/eye administered into the study eye as a single, unilateral dose via intracameral injection on Day 1

Control Group: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Rescue Therapy: Rescue therapy may be allowed in the study eye for a change from baseline in IOP of <20% on any two visits after Day 1 separated by at least 4 weeks. Both the study and non-study eyes may be treated at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

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Randomization/Stratification: No randomization is required as this is an open-label, single arm study.

Visit Schedule: Visit schedule encompasses Screening Visit 1 (Day -49 to -29) followed by 4-week IOP-lowering medication washout period with up to a 2-week additional extension to allow full washout, Baseline Visit 2 (Day -5 to -1), Dosing Visit 3 (Day 1), Treatment Visit 4 (Day 2 + 3 days), Treatment Visit 5 (Day 14 ± 3 days), Treatment Visit 5a (Day 28 ± 3 days), Treatment Visit 6 (Day 42 ± 3 days), Treatment Visit 7 (Day 84 ± 3 days), Treatment Visits 8-15 (every 28 days from Month 4 to Month 11), and Exit Visit 16 (Month 12) for a total of 17 visits. Patients may be exited sooner than Month 12 if they have received rescue therapy, their IOP in the study eye is well-controlled, no implant remnants are visible by gonioscopy during two consecutive visits, and no adverse events (AEs) are present that require continued monitoring.

Study Population Characteristics:

Number of Patients: Following successful screening, approximately 5-10 patients will be dosed into the open-label study.

Condition/Disease: The study population consists of patients with a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma who are currently being treated with a topical PGA in both eyes.

Inclusion Criteria:

1. Male or female between 18 and 85 years of age.
2. Have a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma.
3. Normal appearing anterior chamber angles (Shaffer classification Grade 3 or 4, with an angle of at least 20° determined by gonioscopy, and confirmed to have an open angle as determined by anterior chamber OCT evaluated by a central reading center prior to dosing.
4. Are currently treated with topical PGA for ocular hypertension in both eyes.
5. Patients who in the opinion of the investigator: have an IOP in both eyes that is considered to be adequately controlled at the Screening Visit (Visit 1); can be safely withdrawn from IOP medications in both eyes during the washout period, and who are not considered to be at significant risk for disease progression throughout the trial.
6. At the Baseline Visit after washout (Visit 2), have IOP measurements that meet all of the following:
 - a) Have an IOP at 8:00 a.m. (±30 minutes) and at 10:00 a.m. (±30 minutes) between 22 and 34 mm Hg in both eyes with a ≤4 mm Hg difference between the eyes
 - b) Have an IOP at 4:00 p.m. (±30 minutes) between 19 and 30 mm Hg in both eyes with a ≤4 mm Hg difference between each eye
7. At the Dosing Visit (Visit 3), have IOP measurement that is between 22 and 34 mm Hg in both eyes with a ≤4 mm Hg difference between the eyes.
8. Have endothelial cell counts of at least 2000 cells/mm² and normal endothelial cell morphology prior to dosing as evaluated by central reading center.
9. If female, patients must be incapable of pregnancy because of hysterectomy, tubal ligation or have been amenorrheic for at least 2 years. Female patients must have a negative pregnancy test, and not be nursing.

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If female patient is capable of pregnancy, she must use effective (e.g., double barrier) method of birth control for the duration of the study.

10. Must be able to provide a written informed consent to participate in the study, in accordance with the international Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and local regulations, before initiating any study-related procedures.

Exclusion Criteria:

1. Are diagnosed with closed angle glaucoma, exfoliation syndrome or exfoliation glaucoma, pigment dispersion or secondary glaucoma.
2. Are insufficiently responsive to PGA topical treatment, i.e., are PGA non-responders.
3. Have a history of glaucoma-related surgery (e.g., trabeculectomy, cryotherapy, laser iridotomy and minimally invasive procedures including shunts/stents).
4. Have severe glaucoma with a mean defect (MD) worse than -8.0, a central island of vision, or otherwise severe glaucoma that would not tolerate a short-term increase in IOP.
5. According to the investigator's best judgment, are at risk for progression of glaucoma, VF or VA worsening as a consequence of participation in the trial.
6. Have any abnormality preventing reliable applanation tonometry in either eye.
7. Have a central corneal thickness less than 500 micrometers or greater than 600 micrometers as determined by pachymetry at the Screening Visit (Visit 1).
8. Have a history of recurrent corneal erosion syndrome, multiple corneal abrasions, or an abrasion that was slow to heal.
9. Have had intraocular conventional surgery, intraocular laser surgery, corneal refractive surgery or eyelids surgery within the past 3 months. Complicated cataract surgery that resulted in intraocular lens placement outside the capsular bag or a break in the posterior capsule is not allowed.
10. Are currently diagnosed with active infectious/noninfectious conjunctivitis, or moderate to severe blepharitis in either eye. (Chronic mild blepharitis or injection related to mild blepharitis, lid lag, mild dry eye or seasonal allergies are allowed.)
11. Are currently taking or have taken corticosteroids (oral, ocular, injectable, IV) or used dermatology formulations of steroids in the vicinity of eyes in the 1 month prior to Screening (Visit 1); have a history of chronic ocular corticosteroid (topical or intraocular) use within the past year. Inhaled, intranasal, or topical (dermal) steroids not in the vicinity of the eyes is permissible if on a stable dose for at least 1 month prior to Screening (Visit 1).
12. Have any media opacity or are uncooperative in such a way that restricts adequate examination of the ocular fundus or anterior chamber in either eye.
13. Are unwilling to discontinue use of contact lenses for the duration of their study participation.
14. Have progressive retinal or optic nerve disease apart from glaucoma or history of uveitis or keratitis.
15. Have any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial such as travoprost or poly-lactic acid or similar excipients, topical anesthetic (proparacaine 0.5% or equivalent), iodine, timolol maleate and Vigamox[®] (or generic equivalent).

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16. Have a requirement for any ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Baseline (Visit 2).
17. Have a history, or a suspected history of drug or alcohol dependence in the preceding year.
18. Currently using or used marijuana in the past 30 days prior to Screening (Visit 1).
19. Have received any investigational product within the past 30 days prior to Screening (Visit 1).
20. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same
21. Patients who, per investigator's judgment, are not good clinical trial candidates due to personal (e.g., perceived willingness or ability to comply with protocol, significant traveling distance to medical center) and/or medical (e.g., mental illness, other non-ocular medical conditions, or laboratory abnormalities that might negatively impact trial participation or outcome) conditions that would likely impede the patient's successful study completion or planned analyses.

Response Measures:*Primary Efficacy Measure:*

- Change from baseline in time-matched IOP measurements at Week 2, Week 6, and Week 12 (Day 14, 42, and 84) for study and non-study eye

Secondary Efficacy Measures:

- Change from baseline and percent change from baseline in time-matched IOP measurements for study eye and non-study at all other study time points and visits
- Difference in change from baseline and percent change from baseline in time-controlled IOP measurements between study eye and non-study eye at all study time points and visits
- Cumulative % of study and non-study eyes with at least 20, 25, and 30% reduction in IOP at all study time points and visits
- Cumulative % of patients with IOP <18 at all time points at each study visit
- Mean IOP at all visits all time points

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA
- Visual Field

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- Body system assessment
- Vital signs
- Non fasting clinical laboratory tests (chemistry, hematology, and urinalysis)
- Urine pregnancy tests for females of childbearing potential
- AEs

Pharmacokinetic Measures:

- Systemic exposure to travoprost via analysis of travoprost acid in plasma

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Table 2: Time and Events Schedule, Cohort 2

Note: V16/Month 12 Time and Events Schedule should only be used if patients are not continuing into the Cohort 2 Study Extension 1 and plan to exit the study at V16/Month 12. If the patient is continuing into the Cohort 2 Study Extension 1, V16/Month 12 should follow the Time and Events Schedule in the Cohort 2 Study Extension 1 Synopsis, [Table 3](#).

Procedure	Screening V1 Day -49 to -29	Baseline V2 Day -7 to -1	Dosing V3 Day 1	Treatment V4, 5,5a,6 Day 2,14,28, 42 +/- 3 days	Treatment V7 Day 84 +/- 7 days	Treatment V8,9 Month 4,5 +/- 7 days	Treatment V10 Month 6 +/- 7 days	Treatment V11 Month 7 +/- 7 days	Treatment V12 Month 8 +/- 7 days	Treatment V13 Month 9 +/- 7 days	Treatment V14 Month 10 +/- 7 days	Treatment V15 Month 11 +/- 7 days	Exit/Early Exit ⁸ V16 Month 12 +/- 7 days
Informed consent review	X												
Demographics/ medical & ocular history	X												
Concomitant medication query	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events query	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Pupil measurement	X	X			X		X			X			X
Slit-lamp biomicroscopy	X	X	X ¹	X	X	X	X	X	X	X	X	X	X
Corneal staining	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy photographs (at selected sites)				X ⁷	X	X	X	X	X	X	X	X	X

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Procedure	Screening V1 Day -49 to -29	Baseline V2 Day -7 to -1	Dosing V3 Day 1	Treatment V4, 5,5a,6 Day 2,14,28, 42 +/- 3 days	Treatment V7 Day 84 +/- 7 days	Treatment V8,9 Month 4,5 +/- 7 days	Treatment V10 Month 6 +/- 7 days	Treatment V11 Month 7 +/- 7 days	Treatment V12 Month 8 +/- 7 days	Treatment V13 Month 9 +/- 7 days	Treatment V14 Month 10 +/- 7 days	Treatment V15 Month 11 +/- 7 days	Exit/Early Exit ⁸ V16 Month 12 +/- 7 days
Pachymetry	X	X	X	X	X	X	X		X		X		X
Specular microscopy	X ²	X	X	X	X	X	X		X		X		X ²
Visual field	X												X
Anterior chamber OCT	X				X								X
IOP diurnal curve	X ³	X	X ³	X ⁴	X	X	X	X	X	X	X	X	X
Dilated fundus exam	X	X			X		X						X
Body System Assessment	X				X		X						X
Vitals	X	X			X		X			X			X
Hematology, chemistry and urinalysis	X	X		X ⁵	X		X	X		X			X
Plasma collection for PK analyses		X		X ⁵	X	X	X	X	X	X	X	X	X
Pregnancy test	X	X		X ⁵									X
Study drug administration			X										
Timolol maleate 0.5% distribution and collection ⁶			X	X	X	X	X	X	X	X	X	X	X

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Procedure	Screening V1 Day -49 to -29	Baseline V2 Day -7 to -1	Dosing V3 Day 1	Treatment V4, 5,5a,6 Day 2,14,28, 42 +/- 3 days	Treatment V7 Day 84 +/- 7 days	Treatment V8,9 Month 4,5 +/- 7 days	Treatment V10 Month 6 +/- 7 days	Treatment V11 Month 7 +/- 7 days	Treatment V12 Month 8 +/- 7 days	Treatment V13 Month 9 +/- 7 days	Treatment V14 Month 10 +/- 7 days	Treatment V15 Month 11 +/- 7 days	Exit/Early Exit ⁸ V16 Month 12 +/- 7 days
Exit patient, complete exit form													X

- 1 Slit lamp exam is performed twice during Dosing (Visit 3), before and after ENV515 administration.
- 2 Specular microscopy is needed for all study eyes on all indicated visits; for non-study eyes, it is collected only during Screening (Visit 1) and Exit/Early Exit (Visit 16). Additional measurements may be taken at the investigator’s discretion.
- 3 During Screening (Visit 1) and Dosing (Visit 3), only one IOP timepoint in the morning is needed (see [Section 12](#) for specific time window).
- 4 During Day 2 (Visit 4) and Day 28 (Visit 5a), only the 8 a.m. IOP timepoint is needed. Day 14 (Visits 5) and Day 42 (Visit 6) require full diurnal evaluation.
- 5 Lab and PK samples were not collected at Day 2 (Visit 4) and Day 28 (Visit 5a). Pregnancy test is only required at Day 14 (Visit 5).
- 6 Timolol maleate 0.5% ophthalmic solution is given to the patient to take their first dose in the non-study eye the evening of the their Day 1 Dosing (Visit 3) then dose BID for the remaining portion of the study. Patients will be instructed to return their used bottle(s) at each visit for accountability purposes. A new supply of timolol maleate 0.5% ophthalmic solution will be provided on a monthly basis starting at Day 42 (Visit 6) through Month 11 (Visit 15). During post dose study visits, ensure Timolol maleate 0.5% ophthalmic solution is administered after the 8 AM IOP measurement.
- 7 Gonioscopy photographs are not collected at Day 2 (Visit 4).
- 8 V16/Month 12 Time and Events Schedule should only be used if patients are not continuing into the Cohort 2 Study Extension 1 and plan to exit the study at V16/Month 12. If the patient is continuing into the Cohort 2 Study Extension 1, V16/Month 12 should follow the Time and Events Schedule in the Cohort 2 Study Extension 1 Synopsis, [Table 3](#).

ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 2 EXTENSION 1

Cohort 2 Extension 1 Protocol Synopsis

Investigational Product: ENV515-3 (Travoprost) Intracameral Implant

Phase: 2a Cohort 2 Extension 1

Cohort 2 Study Extension 1 Objective:

- Extend the ENV515-01 Ph2a Cohort 2 study duration beyond 12 months by an additional 6 months to continue evaluation of the ENV515-3 long term safety, efficacy, and biodissolution in patients with bilateral ocular hypertension or primary open-angle glaucoma
-

Clinical Hypotheses:

- A single dose of two ENV515-3 (travoprost) Intracameral Implants will demonstrate end of duration of IOP treatment effect and full biodissolution in the time period between 13 and 18 months
-

Cohort 2 Study Extension 1 Design:

Structure: The Cohort 2 study Extension 1 will extend the ongoing 12 month Cohort 2 by 6 months for a total of 18 months duration for up to 5 patients dosed with a single low dose of ENV515-3 in Cohort 2. The original Cohort 2 of the Phase 2a clinical study was up to 12-month, prospective, open-label, active-comparator-controlled, multi-center study of ENV515-3 (travoprost) Intracameral Implants. The Cohort 2 phase of the study enrolled glaucoma patients to study ENV515 over its entire duration of IOP-lowering efficacy, or up to 12 months after the first dose.

Duration of Patient Participation including study Extension 1: Approximately a maximum of 20 months including up to a 49 day washout period, implantation/treatment administration day, 3 month primary efficacy and safety evaluation period post initial dose of ENV515 in the study eye, a follow-up for 9 months, and 6 month study Extension 1

Study Treatment Investigational Product: ENV515-3 (travoprost) Intracameral Implant

Reference Product: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Dosage/Dose Regimen/Treatment Groups:

ENV515-3 Group: Two ENV515-3 (travoprost) implants/eye administered into the study eye as a single, unilateral dose via intracameral injection on Day 1

Control Group: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Rescue Therapy: Rescue therapy may be allowed in the study eye for a change from baseline in IOP of <20% on any two visits after Day 1 separated by at least 4 weeks. Both the study and non-study eyes may be treated at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

Randomization/Stratification: No randomization is required as this is an open-label, single arm study extension for up to 5 patients who had been dosed in ENV515-01 Cohort 2 study.

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Cohort 2 Study Extension 1 Visit Schedule: Visit schedule encompasses Treatment Visits 17 to 21 (Month 13 and every month thereafter to Month 17) and Exit Visit 22 (Month 18). Patients may be exited sooner than Month 18 if they have received rescue therapy, their IOP in the study eye is well-controlled, no implant remnants are visible by gonioscopy during two consecutive visits, and no treatment related adverse events (AEs) are present that require continued monitoring.

Response Measures in Cohort 2 Study Extension 1 (Month 12 to 18):

Exploratory Efficacy Measure:

- Change from baseline in time-matched 8 AM IOP measurements at Months 13, 14, 15, 16, 17 and 18 for study and non-study eye
- Percent change from baseline in time-matched 8 AM IOP measurements for study eye and non-study at Months 13, 14, 15, 16, 17 and 18
- Difference in change from baseline and percent change from baseline in time-matched 8 AM IOP measurements between study eye and non-study eye at all study time points and visits
- Cumulative % of study and non-study eyes with at least 20, 25, and 30% reduction in 8 AM IOP at all study time points and visits
- Cumulative % of patients with 8 AM IOP <18 at all time points at each study visit
- Mean 8 AM IOP at all visits all time points

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA (ETDRS)
- Visual Field
- Body system assessment
- Vital signs
- Non fasting clinical laboratory tests (chemistry, hematology, urinalysis)
- Urine pregnancy tests for females of childbearing potential
- AEs

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Table 3: Time and Events Schedule, Cohort 2 Extension 1, Months 12 to 18, Including New Schedule for Month 12 Visit for Patients Enrolled in the Cohort 2 Extension 1

Note: If the patient is continuing into the Cohort 2 Study Extension 2, V22/Month 18 should follow the Time and Events Schedule in the Cohort 2 Study Extension 2 Synopsis, [Table 4](#).

Procedure	Treatment V16 Month 12 +/- 7 days	Treatment V17 Month 13 +/- 7 days	Treatment V18 Month 14 +/- 7 days	Treatment V19 Month 15 +/- 7 days	Treatment V20 Month 16 +/- 7 days	Treatment V21 Month 17 +/- 7 days	Exit/Early Exit ⁴ V22 Month 18 +/- 7 days
Informed consent review	X						
Concomitant medication query	X	X	X	X	X	X	X
Adverse events query	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X
Pupil measurement	X		X		X		X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X
Corneal staining	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X
Gonioscopy photographs (at selected sites)	X	X	X	X	X	X	X
Pachymetry	X		X		X		X
Specular microscopy	X ¹		X ¹		X ¹	X ¹	X ¹
Visual field							X
Anterior chamber OCT ³	X					X	X
8 AM IOP	X	X	X	X	X	X	
IOP diurnal curve							X
Dilated fundus exam	X						X
Body System Assessment	X						X
Vitals	X			X			X
Hematology, chemistry and urinalysis	X						X
Plasma collection for PK analyses							X
Urine Pregnancy test							X
Timolol maleate 0.5% distribution and collection ²	X	X	X	X	X	X	X
Exit patient, complete exit form							X

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- ¹ Specular microscopy is needed for all study eyes on all indicated visits; for non-study eyes, it is collected only during Exit/Early Exit (Visit 22). Additional measurements may be taken at the investigator's discretion.
- ² Timolol maleate 0.5% ophthalmic solution is given to the patient to continue dosing BID for the remainder of the study. Patients will be instructed to return their used bottle(s) at each visit for accountability purposes. A new supply of timolol maleate 0.5% ophthalmic solution will be provided on a monthly basis through Month 17 (Visit 21). During post dose study visits, ensure timolol maleate 0.5% ophthalmic solution is administered after the 8 AM IOP measurement.
- ³ Always capture the ENV515 implant(s) in the field of view of at least one OCT image.
- ⁴ V16/Month 12 Time and Events Schedule should only be used if patients are continuing into the Cohort 2 Study Extension 1. If the patients are continuing into the Cohort 2 Study Extension 2, V22/Month 18 should follow the Time and Events Schedule in the Cohort 2 Study Extension 2 Synopsis, [Table 4](#).

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ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 2 EXTENSION 2

Cohort 2 Extension 2 Protocol Synopsis

Investigational Product: ENV515-3 (Travoprost) Intracameral Implant

Phase: 2a Cohort 2 Extension 2

Cohort 2 Study Extension 2 Objective:

- Extend the ENV515-01 Ph2a Cohort 2 study duration beyond 18 months (12 month Cohort 2 + 6 month Extension 1) by an additional 3 months in Extension 2 to continue evaluation of the ENV515-3 long term safety, efficacy, and biodissolution in patients with bilateral ocular hypertension or primary open-angle glaucoma
-

Clinical Hypotheses:

- A single dose of two ENV515-3 (travoprost) Intracameral Implants will demonstrate end of duration of IOP treatment effect and full biodissolution in the time period between 13 and 21 months
-

Cohort 2 Study Extension 2 Design:

Structure: The Cohort 2 study Extension 2 will extend the ongoing 18 month Cohort 2, including 12 month initial study and its 6 month Extension 1, by an additional 3 months for a total of 21 months duration for up to 5 patients dosed with a single low dose of ENV515-3 in Cohort 2. The initial Cohort 2 of the Phase 2a clinical study was up to 12-month, prospective, open-label, active-comparator-controlled, multi-center study of ENV515-3 (travoprost) Intracameral Implants. This 12 month period of Cohort 2 was extended via Extension 1 by up to additional 6 months. The Cohort 2 phase of the study enrolled glaucoma patients to study ENV515 over its entire duration of IOP-lowering efficacy, or up to 12 months after the first dose, all of whom have the option of enrolling sequentially in Extension 1 and 2 for a total of 21 months (12 months of the original Cohort 2 duration, 6 months of the Extension 1, and 3 months of the Extension 2).

Duration of Patient Participation including Cohort 2 Extension 1 and Extension 2: Approximately a maximum of 23 months including up to a 49 day washout period, implantation/treatment administration day, 3 month primary efficacy and safety evaluation period post initial dose of ENV515 in the study eye, follow-up for 9 months, 6 month study Extension 1, and 3 month study Extension 2.

Study Treatment Investigational Product: ENV515-3 (travoprost) Intracameral Implant

Reference Product: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Dosage/Dose Regimen/Treatment Groups:

ENV515-3 Group: Two ENV515-3 (travoprost) implants/eye administered into the study eye as a single, unilateral dose via intracameral injection on Day 1

Control Group: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

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Rescue Therapy: Rescue therapy may be allowed in the study eye for a change from baseline in IOP of <20% on any two visits after Day 1 separated by at least 4 weeks. Both the study and non-study eyes may be treated at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

Randomization/Stratification: No randomization is required as this is an open-label, single arm study extension for up to 5 patients who had been dosed in ENV515-01 Cohort 2 study Extension 1.

Cohort 2 Study Extension 2 Visit Schedule: Visit schedule encompasses Treatment Visits 23 and 24 (Months 19 and 20) and Exit Visit 25 (Month 21). Patients may be exited sooner than Month 21 if they have received rescue therapy, their IOP in the study eye is well-controlled, no implant remnants are visible by gonioscopy during two consecutive visits, and no treatment related adverse events (AEs) are present that require continued monitoring.

Response Measures in Cohort 2 Study Extension 2 (Month 18 to 21):

Exploratory Efficacy Measure:

- Change from baseline in time-matched 8 AM IOP measurements at Months 19, 20 and 21 for study and non-study eye
- Percent change from baseline in time-matched 8 AM IOP measurements for study eye and non-study at Months 19, 20, and 21
- Difference in change from baseline and percent change from baseline in time-matched 8 AM IOP measurements between study eye and non-study eye at all study time points and visits
- Cumulative % of study and non-study eyes with at least 20, 25, and 30% reduction in 8 AM IOP at all study time points and visits
- Cumulative % of patients with 8 AM IOP <18 at all time points at each study visit
- Mean 8 AM IOP at all visits all time points

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA (ETDRS)
- Visual Field
- Body system assessment
- Vital signs
- Non fasting clinical laboratory tests (chemistry, hematology, urinalysis)
- Urine pregnancy tests for females of childbearing potential
- AEs

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Table 4: Time and Events Schedule, Cohort 2 Study Extension 2, Months 18 to 21, Including New Schedule for Month 18 Visit for Patients Enrolled in the Extension 2

Procedure	Treatment V22 Month 18 +/- 7 days	Treatment V23 Month 19 +/- 7 days	Treatment V24 Month 20 +/- 7 days	Exit/Early Exit V25 Month 21 +/- 7 days
Informed consent review	X			
Concomitant medication query	X	X	X	X
Adverse events query	X	X	X	X
BCVA – (ETDRS)	X	X	X	X
Pupil measurement	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X
Corneal staining	X	X	X	X
Gonioscopy	X	X	X	X
Gonioscopy photographs (at selected sites)	X	X	X	X
Pachymetry	X	X	X	X
Specular microscopy	X ¹	X ¹	X ¹	X ¹
Visual field				X
Anterior chamber OCT ³	X	X	X	X
8 AM IOP	X	X	X	
IOP diurnal curve				X
Dilated fundus exam				X
Body System Assessment				X
Vitals				X
Hematology, chemistry and urinalysis				X
Plasma collection for PK analyses				X
Urine Pregnancy test				X
Timolol maleate 0.5% distribution and collection ²	X	X	X	X
Exit patient, complete exit form				X

¹ Specular microscopy is needed for all study eyes on all indicated visits including unscheduled visits; for non-study eyes, it is collected only during Exit/Early Exit (Visit 25).

² Timolol maleate 0.5% ophthalmic solution is given to the patient to continue dosing BID for the remainder of the study. Patients will be instructed to return their used bottle(s) at each visit for accountability purposes. A new supply of timolol maleate 0.5% ophthalmic solution will be provided on a monthly basis through Month 20

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(Visit 24). During post dose study visits, ensure timolol maleate 0.5% ophthalmic solution is administered after the 8 AM IOP measurement.

- ³ Always capture the ENV515 implant(s) in the field of view of at least one OCT image.

ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 3

Cohort 3 Protocol Synopsis

Investigational Product: ENV515-3-2 (Travoprost) Intracameral Implant

Phase: 2a

Study Objective:

- Evaluate the long-term safety, tolerability, and systemic exposure to travoprost following a unilateral, single dose of one or two ENV515-3-2 (travoprost) intracameral implant(s) in the study eye in patients with bilateral ocular hypertension or primary open-angle glaucoma
-

Clinical Hypotheses:

- ENV515-3-2 (travoprost) Intracameral Implants has an acceptable safety profile
-

Study Design:

Structure: Cohort 3 of the Phase 2a clinical study is an up to 12-month, prospective, open-label, active-comparator-controlled, multi-center study of ENV515-3-2 (travoprost) Intracameral Implants. While all cohorts enrolled glaucoma patients, Cohort 1 included patients scheduled for cataract removal and the ENV515 implants were removed after 28 days during cataract surgery. The Cohort 2 phase enrolled patients without the need for cataract surgery in order to study ENV515-3 over its entire duration of IOP-lowering efficacy. Cohort 3 will enroll similar patients as Cohort 2 with similar study design studying ENV515-3-2 over its entire duration of IOP-lowering efficacy. ENV515-3-2 has been reformulated to achieve the same efficacy of two ENV515-3 implants with just one implant and the efficacy of three ENV515-3 implants with just two implants.

Duration of Patient Participation: Approximately 14 months including washout of current PGA therapy, implantation/treatment of investigational product, 3-month primary efficacy and safety evaluation period post dose of ENV515 in the study eye, and followed for an additional 9 months of safety follow-up.

Study Treatment Investigational Product: one or two implant(s) per eye of ENV515-3-2 (travoprost) Intracameral Implant

Reference Product: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Dosage/Dose Regimen/Treatment Groups:

- ENV515-3-2 Low Dose Group: One ENV515-3-2 (travoprost) implant administered into the study eye as a single, unilateral dose via intracameral injection on Day 1
- ENV515-3-2 High Dose Group: Two ENV515-3-2 (travoprost) implants administered into the study eye as a single, unilateral dose via intracameral injection on Day 1
- Control Group: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Rescue Therapy: Rescue therapy may be allowed in the study eye if, in the opinion of the investigator, the IOP is not well controlled on any two visits after Month 3 (Day 84) that are separated by at least 4 weeks (+/- 7 days). Timolol

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maleate 0.5% ophthalmic solution administered BID daily will be used for rescue therapy. The patient should be permanently rescued with Timolol maleate 0.5% ophthalmic solution twice a day until the completion of the study. Notwithstanding the above, both the study and non-study eyes may be rescued at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

Randomization/Stratification: No randomization is conducted as this is an open-label study.

Visit Schedule: Visit schedule encompasses Screening Visit 1 (Day -56 to -42 followed by a 6 week PGA washout period, Baseline Visit 2 (Day -7 to -1), Dosing Visit 3 (Day 1), Treatment Visit 4 (Day 2 + 3 days), Treatment Visit 5 (Day 14 ± 3 days), Treatment Visit 5a (Day 28 ± 3 days), Treatment Visit 6 (Day 42 ± 3 days), Treatment Visit 7 (Day 84 ± 7 days), Treatment Visits 8-15 (every 28 days from Month 4 to Month 11), and Exit Visit 16 (Month 12) for a total of 17 visits. Patients may be exited sooner than Month 12 if they have received rescue therapy, their IOP in the study eye is well-controlled, no implant remnants are visible by gonioscopy during two consecutive visits, and no treatment related adverse events (AEs) are present that require continued monitoring.

Study Population Characteristics:

Number of Patients: Following successful screening and washout, 15 patients in Cohort 3 were dosed with investigational product.

Condition/Disease: The study population consists of patients with a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma who are currently being treated with a topical PGA in both eyes.

Inclusion Criteria:

1. Male or female between 18 and 85 years of age.
2. Have a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma.
3. Normal appearing anterior chamber angles (Shaffer classification Grade 3 or 4, with an angle of at least 20° determined by gonioscopy, and confirmed to have an open angle as determined by anterior chamber OCT evaluated by a central reading center prior to dosing).
4. Are currently treated with topical PGA for ocular hypertension in both eyes. (Dual therapy with PGA (i.e. PGA and another IOP lowering agent) is acceptable)
5. In the opinion of the investigator, the non-study eye can be adequately controlled with timolol maleate 0.5% ophthalmic solution BID.
6. Patients who in the opinion of the investigator, have an IOP in both eyes that is considered to be adequately controlled at Screening (Visit 1), can be safely withdrawn from IOP medications in both eyes during the washout period, and who are not considered to be at significant risk for disease progression throughout the trial.

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7. At the Baseline Visit after washout (Visit 2), have IOP measurements that meet all of the following:
 - a. Have an IOP at 8:00 a.m. (± 30 minutes) and at 10:00 a.m. (± 30 minutes) between 22 and 34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes
 - b. Have an IOP at 4:00 p.m. (± 30 minutes) between 19 and 30 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye
 - c. Demonstrate IOP increase of at least 4 mmHg in each eye at Baseline (Visit 2) compared to the Screening (Visit 1) IOP measurements.
8. At the Dosing Visit (Visit 3), have IOP measurement that is between 22 and 34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes.
9. Have endothelial cell counts of at least 2000 cells/mm² and normal endothelial cell morphology at Screening (Visit 1) as evaluated by central reading center.
10. If female, patients must either be incapable of pregnancy because of hysterectomy, tubal ligation or have been amenorrheic for at least 2 years or must use effective (e.g., double barrier) method of birth control for the duration of the study. Female patients must have a negative pregnancy test and not be nursing.
11. Must be able to provide a written informed consent to participate in the study, in accordance with the international Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and local regulations, before initiating any study-related procedures.

Exclusion Criteria:

1. Are diagnosed with closed angle glaucoma, exfoliation syndrome or exfoliation glaucoma, pigment dispersion or secondary glaucoma.
2. Are insufficiently responsive to PGA topical treatment, i.e., are PGA non-responders.
3. Have a history of glaucoma-related surgery (e.g., Selective Laser Trabeculoplasty (SLT), Argon Laser Trabeculoplasty (ALT), trabeculectomy, cryotherapy, laser iridotomy and minimally invasive procedures including shunts/stents) in the study eye.
4. Have severe glaucoma with a mean defect (MD) worse than -8.0, a central island of vision, or otherwise severe glaucoma that would not tolerate a short-term increase in IOP including advanced cupping.
5. Have manifest refraction BCVA worse than 20/80 Snellen in either eye as measured using ETDRS chart.
6. Have hyperemia score of 1 or greater at Baseline (Visit 2)
7. According to the investigator's best judgment, are at risk for progression of glaucoma, VF or VA worsening as a consequence of participation in the trial in either eye.
8. Have any abnormality preventing reliable applanation tonometry in either eye.
9. Have a central corneal thickness less than 500 micrometers or greater than 600 micrometers as determined by pachymetry at Screening (Visit 1) in either eye.
10. Have a history of recurrent corneal erosion syndrome, multiple corneal abrasions, or an abrasion that was slow to heal in either eye.
11. Have had intraocular conventional surgery, intraocular laser surgery, corneal refractive surgery or eyelids surgery within the past 3 months in the study eye. Complicated cataract surgery that resulted in intraocular lens placement outside the capsular bag or a break in the posterior capsule is not allowed.

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12. Are currently diagnosed with active infectious/noninfectious conjunctivitis, or moderate to severe blepharitis in either eye. (Chronic mild blepharitis or injection related to mild blepharitis, lid lag, mild dry eye or seasonal allergies are allowed.)
13. Are currently taking or have taken corticosteroids (oral, ocular, injectable, IV) or used dermatology formulations of steroids in the vicinity of eyes in the 1 month prior to Screening (Visit 1); have a history of chronic ocular corticosteroid (topical or intraocular) use within the past year. Inhaled, intranasal, or topical (dermal) steroids not in the vicinity of the eyes is permissible if on a stable dose for at least 1 month prior to Screening (Visit 1).
14. Have any media opacity or are uncooperative in such a way that restricts adequate examination of the ocular fundus or anterior chamber in either eye.
15. Are unwilling to discontinue use of contact lenses for the duration of their study participation.
16. Have progressive retinal or optic nerve disease apart from glaucoma or history of uveitis or keratitis.
17. Have any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial such as travoprost or poly-lactic acid or similar excipients, topical anesthetic (proparacaine 0.5% or equivalent), iodine, timolol maleate, and VIGAMOX[®] (or generic equivalent).
18. Have a requirement for any ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Baseline (Visit 2).
19. Have a history, or a suspected history of illicit drug or alcohol dependence in the preceding year.
20. Currently using or used marijuana in the past 30 days prior to Screening (Visit 1).
21. Have received any investigational product within the past 30 days prior to Screening (Visit 1) or have ever been previously implanted in the anterior segment with experimental therapies.
22. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same
23. Patients who, per investigator's judgment, are not good clinical trial candidates due to personal (e.g., perceived willingness or ability to comply with protocol, significant traveling distance to medical center) and/or medical (e.g., mental illness, other non-ocular medical conditions, or laboratory abnormalities that might negatively impact trial participation or outcome) conditions that would likely impede the patient's successful study completion or planned analyses.

Response Measures:

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)

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- BCVA
- Visual Field
- Body system assessment
- Vital signs
- Non fasting clinical laboratory tests (chemistry and hematology)
- Urine pregnancy tests for females of childbearing potential
- AEs

Pharmacokinetic Measures:

- Systemic exposure to travoprost via analysis of travoprost acid in plasma

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Table 5: Time and Events Schedule, Cohort 3¹¹

Note: V16/Month 12 Time and Events Schedule should only be used if patients are not continuing into the Cohort 3 Study Extension 1 and plan to exit the study at V16/Month 12. If the patient is continuing into the Cohort 3 Study Extension 1, V16/Month 12 should follow the Time and Events Schedule in the Cohort 3 Study Extension 1 Synopsis, [Table 6](#).

Procedure	Screening V1 Day -56 to -42	Baseline V2 Day -7 to -1	Dosing V3 Day 1	Treatment V4, 5,5a,6 Day 2,14,28, 42 +/- 3 days	Treatment V7 Day 84 +/- 7 days	Treatment V8,9 Month 4,5 +/- 7 days	Treatment V10 Month 6 +/- 7 days	Treatment V11 Month 7 +/- 7 days	Treatment V12 Month 8 +/- 7 days	Treatment V13 Month 9 +/- 7 days	Treatment V14 Month 10 +/- 7 days	Treatment V15 Month 11 +/- 7 days	Exit/Early Exit V16 Month 12 +/- 7 days
Informed consent review	X												
Demo-graphics/ medical & ocular history	X												
Eligibility Criteria Confirmation Prior to Dosing	X	X	X										
Concomitant medication query	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events query	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA – (ETDRS) With manifest refraction	X	X	X	X	X	X	X	X	X	X	X	X	X
Pupil measurement	X	X		X ¹	X	X	X	X	X				
Slit lamp biomicroscopy	X	X	X ²	X	X	X	X	X	X	X	X	X	X
Corneal staining	X	X	X	X	X	X	X	X	X				
8 AM IOP	X ³		X ³							X	X	X	X ³

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Procedure	Screening V1 Day -56 to -42	Baseline V2 Day -7 to -1	Dosing V3 Day 1	Treatment V4, 5,5a,6 Day 2,14,28, 42 +/- 3 days	Treatment V7 Day 84 +/- 7 days	Treatment V8,9 Month 4,5 +/- 7 days	Treatment V10 Month 6 +/- 7 days	Treatment V11 Month 7 +/- 7 days	Treatment V12 Month 8 +/- 7 days	Treatment V13 Month 9 +/- 7 days	Treatment V14 Month 10 +/- 7 days	Treatment V15 Month 11 +/- 7 days	Exit/Early Exit V16 Month 12 +/- 7 days
IOP diurnal curve		X		X ⁴	X	X	X	X	X				
Gonioscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy photographs (at selected sites)				X ⁵	X	X	X	X	X	X	X	X	X
Pachymetry	X	X		X	X	X	X	X	X	X	X	X	X
Corneal photography (at selected sites)		X											
Specular microscopy ⁶	X ⁶	X ⁶		X	X	X	X	X	X	X	X	X	X
Visual field	X												X
Anterior chamber OCT ¹⁰	X			X ¹²	X	X	X	X	X	X	X	X	X
Dilated fundus exam	X	X			X		X						X
Body System Assessment	X				X		X						X
Vitals	X	X			X		X						X
Hematology, chemistry and urinalysis	X	X			X		X						X
PK sampling		X		X ⁷	X	X	X	X	X				
Pregnancy test	X	X											X

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Procedure	Screening V1 Day -56 to -42	Baseline V2 Day -7 to -1	Dosing V3 Day 1	Treatment V4, 5,5a,6 Day 2,14,28,42 +/- 3 days	Treatment V7 Day 84 +/- 7 days	Treatment V8,9 Month 4,5 +/- 7 days	Treatment V10 Month 6 +/- 7 days	Treatment V11 Month 7 +/- 7 days	Treatment V12 Month 8 +/- 7 days	Treatment V13 Month 9 +/- 7 days	Treatment V14 Month 10 +/- 7 days	Treatment V15 Month 11 +/- 7 days	Exit/Early Exit V16 Month 12 +/- 7 days
Study drug administration			X										
Timolol maleate 0.5% distribution and collection ⁸			X	X	X	X	X	X	X	X	X	X	X
Rescue therapy with timolol (if eligible)					X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X	X	X	
Exit patient, complete exit form													X

¹ Pupil measurement required only at Visit 5 (Day 14).

² Slit lamp exam is performed twice during Day 1 Dosing (Visit 3), before and after ENV515 administration.

³ During Screening (Visit 1), Day 1 Dosing (Visit 3) and Month 12 Exit/Early Exit (Visit 16), only one IOP timepoint in the morning is needed (see [Section 13](#) for specific time windows).

⁴ During Day 2 (Visit 4) only the 8 a.m. IOP timepoint is needed. Day 14 (Visit 5), Day 28 (Visit 5a) and Day 42 (Visit 6) require full diurnal evaluation.

⁵ Gonioscopy photographs are not collected at Day 2 (Visit 4).

⁶ Specular microscopy is needed for all study eyes on indicated visits; for non-study eyes, it is collected only during Screening (Visit 1) and Baseline (Visit 2). Additional measurements may be taken at the investigator's discretion.

⁷ PK sampling not required at Day 2 (Visit 4).

⁸ Timolol maleate 0.5% ophthalmic solution is given to the patient to take their first dose in the non-study eye the evening of their Day 1 Dosing (Visit 3) then dose BID for the duration of the study. Patients will be instructed to return their used bottle(s) at each visit for accountability purposes. A new supply of timolol maleate 0.5% ophthalmic solution will be provided on a monthly basis starting at Day 28 (Visit 5a) through Month 11 (Visit 15). During post dose study visits, ensure that timolol maleate 0.5% ophthalmic solution is administered after the 8 a.m. IOP measurement.

⁹ Patient can only be rescued after all diurnal IOP measurements have been collected for the visit.

¹⁰ Capture the ENV515 implant(s) in the field of view of at least one OCT image.

¹¹ Due to Amendment 7, some patients may not have all assessments performed as they have already completed the visits where assessments were added.

¹² Collect OCT images during visits 5, 5a and 6. No OCT images should be collected during Visit 4.

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ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 3 EXTENSION 1**Cohort 3 Extension 1 Protocol Synopsis**

Investigational Product: ENV515-3-2 (Travoprost) Intracameral Implant

Phase: 2a Cohort 3 Extension 1

Cohort 3 Study Extension 1 Objective:

- Extend the 12-month ENV515-01 Ph2a Cohort 3 study duration by an additional 6 months in Cohort 3 Extension 1 to continue evaluation of the ENV515-3-2 long term safety and biodissolution in patients with bilateral ocular hypertension or primary open-angle glaucoma
-

Clinical Hypotheses:

- ENV515-3-2 (travoprost) Intracameral Implants has an acceptable safety profile
-

Cohort 3 Study Extension 1 Design:

Structure: The Cohort 3 Extension 1 extended the ongoing 12 month Cohort 3, including both dose arms of the low and high doses of ENV515-3-2, by an additional 6 months for a total of 18 months duration for 15 patients. The initial Cohort 3 of the Phase 2a clinical study was up to 12-month, prospective, open-label, active-comparator-controlled, multi-center study of ENV515-3-2 (travoprost) Intracameral Implants. The Cohort 3 phase of the study enrolled glaucoma patients to study ENV515 over its entire duration of IOP-lowering efficacy, or up to 12 months after the first dose, all of whom have the option of enrolling in Cohort 3 Extension 1 for a total of 18 months (12 months of the original Cohort 3 duration and 6 months of the Cohort 3 Extension 1). The Cohort 3 investigational product, ENV515-3-2 implant, has been reformulated to achieve the same efficacy of two ENV515-3 implants studied in Cohort 2 with just one implant and the efficacy of three ENV515-3 implants with just two implants.

Duration of Patient Participation including Cohort 3 Extension 1: Approximately a maximum of 20 months including up to a 56 day screening and washout periods, implantation/treatment administration day, a 3 month primary efficacy and safety evaluation period post initial dose of ENV515 in the study eye, follow-up for 9 months, and an additional 6 month Cohort 3 Extension 1.

Study Treatment Investigational Product: one or two implant(s) per eye of ENV515-3-2 (travoprost) Intracameral Implant

Reference Product: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Dosage/Dose Regimen/Treatment Groups:

- ENV515-3-2 Low Dose Group: One ENV515-3-2 (travoprost) implant administered into the study eye as a single, unilateral dose via intracameral injection on Day 1
- ENV515-3-2 High Dose Group: Two ENV515-3-2 (travoprost) implants administered into the study eye as a single, unilateral dose via intracameral injection on Day 1
- Control Group: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

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Rescue Therapy: Rescue therapy may be allowed in the study eye if, in the opinion of the investigator, the IOP is not well controlled on any two visits after Month 3 (Day 84) that are separated by at least 4 weeks (+/- 7 days). Timolol maleate 0.5% ophthalmic solution administered BID daily will be used for rescue therapy. The patient should be permanently rescued with Timolol maleate 0.5% ophthalmic solution twice a day until the completion of the study. Notwithstanding the above, both the study and non-study eyes may be rescued at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

Randomization/Stratification: No randomization is required as this is an open-label, two arm study Extension 1 for 15 patients who had been dosed in ENV515-01 Ph2a Cohort 3 study.

Cohort 3 Extension 1 Visit Schedule: Visit schedule encompasses Treatment Visits 17 to 21 (Month 13 and every month thereafter to Month 17) and Exit Visit 22 (Month 18). Patients may be exited sooner than Month 18 if they have received rescue therapy, their IOP in the study eye is well-controlled, no implant remnants are visible by gonioscopy during two consecutive visits, and no treatment related adverse events (AEs) are present that require continued monitoring.

Response Measures in Cohort 3 Study Extension 1 (Month 13 to 18):

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA (ETDRS)
- Visual Field
- Body system assessment
- Vital signs
- Non fasting clinical laboratory tests (chemistry, hematology, urinalysis)
- Urine pregnancy tests for females of childbearing potential
- AEs

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Table 6: Time and Events Schedule, Cohort 3 Extension 1, Months 12 to 18, Including New Schedule for Month 12 Visit for Cohort 3 Patients Enrolled in the Cohort 3 Extension 1

Note: If the patient is continuing into the Cohort 3 Extension 2, V22/Month 18 should follow the Time and Events Schedule in the Cohort 3 Extension 2 Synopsis, [Table 7](#).

Procedure	Treatment V16 Month 12 +/- 7 days ⁴	Treatment V17 Month 13 +/- 7 days	Treatment V18 Month 14 +/- 7 days	Treatment V19 Month 15 +/- 7 days	Treatment V20 Month 16 +/- 7 days	Treatment V21 Month 17 +/- 7 days	Exit/Early Exit V22 Month 18 +/- 7 days
Informed consent review	X						
Concomitant medication query	X	X	X	X	X	X	X
Adverse events query	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X
8 AM IOP	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X
Gonioscopy photographs (at selected sites)	X	X	X	X	X	X	X
Pachymetry	X	X	X	X	X	X	X
Specular microscopy	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X
Visual field							X
Anterior chamber OCT ³	X	X	X	X	X	X	X

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Procedure	Treatment V16 Month 12 +/- 7 days ⁴	Treatment V17 Month 13 +/- 7 days	Treatment V18 Month 14 +/- 7 days	Treatment V19 Month 15 +/- 7 days	Treatment V20 Month 16 +/- 7 days	Treatment V21 Month 17 +/- 7 days	Exit/Early Exit V22 Month 18 +/- 7 days
Dilated fundus exam							X
Body System Assessment							X
Vitals							X
Hematology, chemistry and urinalysis							X
Urine Pregnancy test							X
Timolol maleate 0.5% distribution and collection ²	X	X	X	X	X	X	X
Exit patient, complete exit form							X

¹ Specular microscopy is needed for all study eyes on all indicated visits. Additional measurements may be taken at the investigator's discretion.

² Timolol maleate 0.5% ophthalmic solution is given to the patient to continue dosing BID for the remainder of the study. Patients will be instructed to return their used bottle(s) at each visit for accountability purposes. A new supply of timolol maleate 0.5% ophthalmic solution will be provided on a monthly basis through Month 17 (Visit 21). During post dose study visits, ensure timolol maleate 0.5% ophthalmic solution is administered after the 8 AM IOP measurement.

³ Capture the ENV515 implant(s) in the field of view of at least one OCT image.

⁴ V16/Month 12 Time and Events Schedule should only be used if patients are continuing into the Cohort 3 Study Extension 1. If the patients are continuing into the Cohort 3 Extension 2, V22/Month 18 should follow the Time and Events Schedule in the Cohort 3 Extension 2 Synopsis, [Table 7](#).

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ENV515-01 PHASE 2A CLINICAL STUDY, COHORT 3 EXTENSION 2

Cohort 3 Extension 2 Protocol Synopsis

Investigational Product: ENV515-3-2 (Travoprost) Intracameral Implant

Phase: 2a Cohort 3 Extension 2

Cohort 3 Study Extension 2 Objective:

- Extend the 18-month ENV515-01 Ph2a Cohort 3 study duration by an additional 6 months in Cohort 3 Extension 2 to continue evaluation of the ENV515-3-2 long term safety and biodissolution in patients with bilateral ocular hypertension or primary open-angle glaucoma
-

Clinical Hypotheses:

- ENV515-3-2 (travoprost) Intracameral Implants has an acceptable safety profile
-

Cohort 3 Study Extension 2 Design:

Structure: The Cohort 3 Extension 2 is extending the ongoing 18 month Cohort 3, including both dose arms of the low and high doses of ENV515-3-2, by an additional 6 months for a total of 24 months duration for up to 15 patients. The initial Cohort 3 of the Phase 2a clinical study was up to 12-month, prospective, open-label, active-comparator-controlled, multi-center study of ENV515-3-2 (travoprost) Intracameral Implants. The Cohort 3 phase of the study enrolled glaucoma patients to study ENV515 over its entire duration of IOP-lowering efficacy, or up to 12 months after the first dose, all of whom had the option of enrolling in Cohort 3 Extension 1 for a total of 18 months (12 months of the original Cohort 3 duration and 6 months of the Cohort 3 Extension 1). The Cohort 3 investigational product, ENV515-3-2 implant, has been reformulated to achieve the same efficacy of two ENV515-3 implants studied in Cohort 2 with just one implant and the efficacy of three ENV515-3 implants with just two implants.

Duration of Patient Participation including Cohort 3 Extension 2: Approximately a maximum of 26 months including up to a 56 day screening and washout periods, implantation/treatment administration day, a 3 month primary efficacy and safety evaluation period post initial dose of ENV515 in the study eye, follow-up for 9 months, additional 6 month Cohort 3 Extension 1, and an additional 6 month Cohort 3 Extension 2.

Study Treatment Investigational Product: one or two implant(s) per eye of ENV515-3-2 (travoprost) Intracameral Implant

Reference Product: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

Dosage/Dose Regimen/Treatment Groups:

- ENV515-3-2 Low Dose Group: One ENV515-3-2 (travoprost) implant administered into the study eye as a single, unilateral dose via intracameral injection on Day 1
- ENV515-3-2 High Dose Group: Two ENV515-3-2 (travoprost) implants administered into the study eye as a single, unilateral dose via intracameral injection on Day 1
- Control Group: Timolol maleate 0.5% ophthalmic solution administered BID daily in the non-study eye

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Rescue Therapy: Rescue therapy may be allowed in the study eye if, in the opinion of the investigator, the IOP is not well controlled on any two visits after Month 3 (Day 84) that are separated by at least 4 weeks (+/- 7 days). Timolol maleate 0.5% ophthalmic solution administered BID daily will be used for rescue therapy. The patient should be permanently rescued with Timolol maleate 0.5% ophthalmic solution twice a day until the completion of the study. Notwithstanding the above, both the study and non-study eyes may be rescued at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

Randomization/Stratification: No randomization is required as this is an open-label, two arm study Extension 2 for 15 patients who had been dosed in ENV515-01 Ph2a Cohort 3 study.

Cohort 3 Extension 2 Visit Schedule: Visit schedule encompasses Treatment Visits 22 to 27 (Month 18 and every month thereafter to Month 23) and Exit Visit 28 (Month 24). Patients may be exited sooner than Month 24 if they have received rescue therapy, their IOP in the study eye is well-controlled, no implant remnants are visible by gonioscopy during two consecutive visits, and no treatment related adverse events (AEs) are present that require continued monitoring.

Response Measures in Cohort 3 Study Extension 2 (Months 18 to 24):

Safety Measures: Assessed by evaluating changes from baseline in the following:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA (ETDRS)
- Visual Field
- Body system assessment
- Vital signs
- Non fasting clinical laboratory tests (chemistry, hematology, urinalysis)
- Urine pregnancy tests for females of childbearing potential
- AEs

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Table 7: Time and Events Schedule, Cohort 3 Extension 2, Months 18 to 24, Including New Schedule for Month 18 Visit for Cohort 3 Patients Enrolled in the Cohort 3 Extension 2

Procedure	Treatment V22 Month 18 +/- 7 days ¹	Treatment V23 Month 19 +/- 7 days	Treatment V24 Month 20 +/- 7 days	Treatment V25 Month 21 +/- 7 days	Treatment V26 Month 22 +/- 7 days	Treatment V27 Month 23 +/- 7 days	Exit/Early Exit V28 Month 24 +/- 7 days
Informed consent review	X						
Concomitant medication query	X	X	X	X	X	X	X
Adverse events query	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X
8 AM IOP	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X
Gonioscopy photographs (at selected sites)	X	X	X	X	X	X	X
Pachymetry	X	X	X	X	X	X	X
Specular microscopy	X ²	X ²	X ²	X ²	X ²	X ²	X
Visual field							X
Anterior chamber OCT ³	X	X	X	X	X	X	X
Dilated fundus exam							X
Body System Assessment							X

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Procedure	Treatment V22 Month 18 +/- 7 days ¹	Treatment V23 Month 19 +/- 7 days	Treatment V24 Month 20 +/- 7 days	Treatment V25 Month 21 +/- 7 days	Treatment V26 Month 22 +/- 7 days	Treatment V27 Month 23 +/- 7 days	Exit/Early Exit V28 Month 24 +/- 7 days
Vitals							X
Hematology, chemistry and urinalysis							X
Urine Pregnancy test							X
Timolol maleate 0.5% distribution and collection ⁴	X	X	X	X	X	X	X
Exit patient, complete exit form							X

¹ V22/Month 18 Time and Events Schedule should only be used if patients are continuing into the Cohort 3 Study Extension 2.

² Specular microscopy is needed for all study eyes on all indicated visits. Additional measurements may be taken at the investigator's discretion.

³ Timolol maleate 0.5% ophthalmic solution is given to the patient to continue dosing BID for the remainder of the study. Patients will be instructed to return their used bottle(s) at each visit for accountability purposes. A new supply of timolol maleate 0.5% ophthalmic solution will be provided on a monthly basis through Month 23 (Visit 27). During post dose study visits, ensure timolol maleate 0.5% ophthalmic solution is administered after the 8 AM IOP measurement.

⁴ Capture the ENV515 implant(s) in the field of view of at least one OCT image.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Argon Laser Trabeculoplasty
BCVA	Best Corrected Visual Acuity
CME	Cystoid Macular Edema
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
ENV515-1	Envisia Therapeutics designation for Intracameral Implant containing 42.5 µg travoprost
ENV515-3	Envisia Therapeutics designation for Intracameral Implant containing 14.1 µg travoprost
ENV515-3-2	Envisia Therapeutics designation for Intracameral Implant containing 26.1 µg travoprost
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-To-Treat
LogMAR	Logarithm of the Minimum Angle of Resolution
MD	Mean Defect (as in visual field test)
MedDRA	Medical Dictionary for Regulatory Activities
MIG	Minimally Invasive Glaucoma implants
NOAEL	No-Observed Adverse Effect Level

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Abbreviation or Specialist Term	Explanation
NSE	Non-Study Eye
OCT	Optical Coherence Tomography
PGA	Prostaglandin Analogue
PK	Pharmacokinetic(s)
PLA	poly(D,L-lactide)
PLGA	poly(lactic-co-glycolic acid)
RGP	Rigid Gas Permeable (lenses)
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SE	Study Eye
SITA	Swedish Interactive Threshold Algorithms
SOP	Standard Operating Procedures
SLT	Selective Laser Trabeculoplasty
TBD	To Be Determined
TM	Trabecular Meshwork
VA	Visual Acuity
VF	Visual Field

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1. INTRODUCTION

Glaucoma is a progressive optic neuropathy affecting more than 3 million Americans over the age of 39 and is a leading cause of blindness in adults over age 60. According to the National Eye Institute, more than 120,000 Americans are blind due to glaucoma (3, 4). Elevated intraocular pressure (IOP) is the most important risk factor for the development of glaucoma and is a result of abnormally high resistance to aqueous humor drainage through the trabecular meshwork (TM), a multi-laminar array of collagen beams covered by endothelial-like cells.

Due to limited understanding of the pathophysiology of the optic neuropathy characteristic of glaucoma, current glaucoma therapies are focused on reducing IOP. The prostaglandin analogues (PGAs) are currently the most prescribed class of topical therapies for ocular hypertension or glaucoma in the United States, with latanoprost, travoprost, and bimatoprost being used most frequently. However, their use has been limited by several shortcomings.

First, the compliance with existing glaucoma topical therapies is generally low, with 30% to 60% of patients discontinuing the therapy within the first year of treatment. Second, topical ophthalmic agents currently in use have local and systemic side effects (e.g., a relatively high incidence of hyperemia for topical PGAs, including travoprost). Third, the once a day administration of PGAs, accompanied by drug level peaks and troughs in the aqueous humor and the surrounding tissues, potentially leads to 24-hour IOP fluctuations that may contribute to accelerated loss of visual field (VF) in susceptible patients (5). Lastly, the combination of these factors has been shown to increase the cost of patient care due to more rapid disease progression.

Therefore, an alternative treatment using an extended-release delivery system with an improved safety/efficacy profile would be a welcome addition to the current pharmacological armamentarium. To date, there are no approved anti-glaucoma therapies that provide an extended-release of a pharmacological agent directly to the site of action. Development of an extended-release PGA formulation administered directly into the anterior chamber would likely improve both compliance and the adverse event (AE) profile of current PGA and other IOP lowering therapies.

ENV515 (travoprost) Intracameral Implant is a biodegradable, extended-release formulation containing travoprost (1, 2) in a poly(D,L-lactide) (PLA) biodegradable polymer drug delivery system. Studies in preclinical models with ENV515 formulations have shown sustained IOP lowering efficacy lasting up to 8 months following a single dose, combined with acceptable safety and tolerability profiles. This body of knowledge, pointing to a potential for improved compliance, ocular surface tolerability, and possibly long-term beneficial outcomes, makes ENV515 extended-release travoprost therapy a promising area of research and development.

1.1. Description of Investigational Product

ENV515 is formulated with travoprost in a biodegradable PLA polymer drug delivery system composed of a PLA blend of R203S and R208 polymers. PLA and its closely related (poly(lactic-co-glycolic acid)) PLGA polymers are used in many FDA-approved products and are hydrolyzed in the body to lactic acid and glycolic acid.

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Additional information about ENV515, including nonclinical and clinical findings, and known and potential risks and benefits to human subjects, may be found in the Investigator's Brochure.

The clinical trial formulation is an aseptically produced, single-dose, ENV515 (travoprost) Intracameral Implant composed of a biodegradable, extended-release dosage form containing the PGA travoprost and biodegradable PLA polymer. ENV515 is formulated as a solid, rod shaped implant in 3 different sizes:

- ~225 μm x ~225 μm x ~2,925 μm implant with 42.5 μg of travoprost/implant referenced as ENV515-1 (used in Cohort 1)
- ~150 μm x ~150 μm x ~1,500 μm implant with 14.1 μg of travoprost/implant referenced as ENV515-3, (used in Cohorts 1 and 2)
- ~200 μm x ~200 μm x ~1,500 μm implant with 26.1 μg of travoprost/implant referenced as ENV515-3-2 (to be used in Cohort 3)

Based on the results from Cohort 1 in which both ENV515-1 and ENV515-3 implants sizes were administered, only the smaller-sized implant with a lower dose of travoprost, ENV515-3, was advanced into Cohort 2. ENV515-3 and its variant ENV515-3-2, are studied in the Cohorts 2 and 3 of this trial, respectively.

ENV515-3-2 has been formulated to achieve the same efficacy as two ENV515-3 implants with just one implant and the efficacy of three ENV515-3 implants with just two implants:

- Low dose: 28.2 μg via two ENV515-3 implants in Cohorts 1 and 2 or 26.1 μg via one ENV515-3-2 implants in Cohort 3
- High dose: 42.3 μg via three ENV515-3 implants in Cohort 1 or 52.2 μg via two ENV515-3-2 implants in Cohort 3

Thus Cohort 3 was designed to replicate the low dose from Cohort 2 with a single ENV515-3-2 implant per eye, and to dose escalate from Cohort 2 to a high dose achieved via two ENV515-3-2 implants per eye. Specifically, while two implants/eye of ENV515-3 dosed in low dose Cohort 2 delivered 28.2 μg of travoprost/eye, and 1 implant per eye of ENV515-3-2 to be dosed in low dose of Cohort 3 will deliver 26.1 μg of travoprost/eye. 2 implants/eye of ENV515-3-2 to be dosed in high dose of Cohort 3 will deliver 52.2 μg of travoprost/eye.

In Cohort 1 of this clinical study, the doses of travoprost in the ENV515 drug product used were:

- 28.2 μg (two ENV515-3 implants)
- 42.3 μg (three ENV515-3 implants)
- 42.5 μg (one ENV515-1 implant)
- 85.0 μg (two ENV515-1 implants).

In Cohort 2 of this clinical study, the dose of travoprost in the ENV515-3 investigational product used was:

- 28.2 μg (two ENV515-3 implants).

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In Cohort 3 of this clinical study, the dose of travoprost in the ENV515-3-2 investigational product used will be:

- 26.1 µg (one ENV515-3-2 implant)
- 52.2 µg (two ENV515-3-2 implants).

All investigational product implants will be loaded into a single use sterile applicator in a sterile field immediately prior to dosing and delivered directly into the anterior chamber of the eye via intracameral injection.

ENV515 investigational product is packaged in a sterile glass vial with an overseal containing one implant/vial (ENV515-1, ENV515-3, or ENV515-3-2). Four or five vials containing ENV515 investigational product will be provided in each clinical trial material kit to allow for applicator loading overage. One sterile ENV515 implant applicator per each clinical trial material kit will be provided in a sterile pouch.

There is no placebo formulation in this study. In Cohort 1, the non-study eye was dosed with TRAVATAN Z (travoprost ophthalmic solution) 0.004% administered as indicated (one eye drop once a day). TRAVATAN Z was provided in its original packaging.

In Cohorts 2 and 3, the non-study eye will be dosed with timolol maleate 0.5% ophthalmic solution (8), the comparator typically used in registration studies, administered as indicated (one eye drop twice a day). Timolol maleate 0.5% ophthalmic solution will be provided in its original packaging.

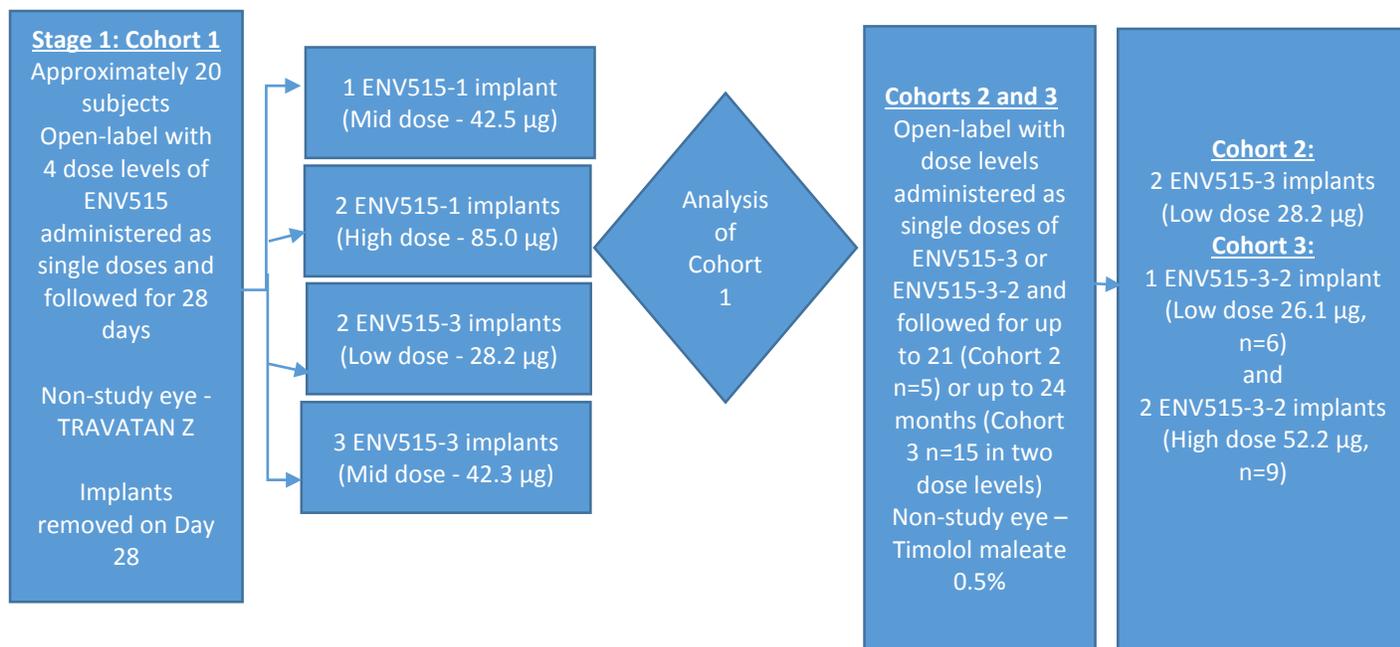
1.2. Overall Trial Design

ENV515-01 is a multicenter, open-label, prospective, active-comparator-controlled Phase 2a study of ENV515 (travoprost) Intracameral Implant comprising of three stages:

- The completed Cohort 1 was a 28-day study focused on evaluation of the initial safety, efficacy and pharmacokinetic properties of ENV515 conducted in glaucoma patients scheduled for cataract removal during which the ENV515 implant is removed during the cataract procedure 28 days after implantation;
- The ongoing Cohort 2 is a 12-month study with a 6-month optional Extension 1 followed by an additional 3-month optional Extension 2 (for up to a total of 21 months) which is focused on evaluation of the long-term safety and efficacy in glaucoma patients during which the two ENV515-3 implants are followed through their biodissolution while the duration of IOP-lowering efficacy is assessed;
- Cohort 3 is a 12-month study with a 6-month optional Extension 1 focused on evaluation of the long-term safety in glaucoma patients during which one or two ENV515-3-2 implants per study eye are followed through their biodissolution.

To date, Cohorts 1 and 2 of the study have been completed for 4 dose levels of ENV515.

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Figure 1: Overall Study Design


1.3. Justification for Route of Administration and Dose Selection

The initial 28-day Cohort 1 was designed to assess the initial safety, tolerability, effect on IOP, aqueous humor pharmacokinetics (PK), systemic exposure, and remaining travoprost in ENV515 implants at 4 dose levels of travoprost: 28.2 µg, 42.3 µg, 42.5 µg, and 85.0 µg/eye. The 4 dose levels were achieved via 2 different implant sizes of the same formulation, with smaller sized ENV515-3 and a larger sized ENV515-1. The Cohort 1 phase of the study was conducted as a multicenter, randomized, open-label, parallel-group, dose-ranging, 28-day trial in 21 patients with bilateral open-angle glaucoma or ocular hypertension who were scheduled for upcoming cataract surgery in a single eye. ENV515 implants were administered unilaterally in the study eye (pre-surgical eye) 4 weeks prior to the planned cataract surgery and were retrieved during cataract surgery.

The actual Cohort 1 treatment groups and dose levels were as follows:

- Two patients dosed with one ENV515-1 implant (42.5 µg)
- Two patients dosed with two ENV515-1 implants (85.0 µg)
- Seven patients dosed with two ENV515-3 implants (28.2 µg)
- Ten patients dosed with three ENV515-3 implants (42.3 µg)

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Following the completion of Cohort 1, the ongoing 12-month Cohort 2 with 6-month optional Extension 1 followed by an additional 3-month optional Extension 2 (for up to a total of 21 months) was initiated to assess the long-term safety, tolerability, effect on IOP, and systemic exposure of a single travoprost dose of 28.2 µg achieved via two ENV515-3 implants.

The actual Cohort 2 treatment group and dose level is as follows:

- Five patients dosed with two ENV515-3 implant (28.2 µg)

Following the completion of the interim 6-month analysis of the ongoing Cohort 2, Cohort 3 is designed as a two dose level cohort consisting of a low and high dose groups. In Cohort 3, the low dose is achieved via a single ENV515-3-2 implant per eye vs. two ENV515-3 implants per eye in the low dose in Cohort 2. The high dose in Cohort 3 is achieved via two ENV515-3-2 implants per eye. Cohort 3 will thus assess the long-term safety, tolerability, effect on IOP, and systemic exposure of a single travoprost dose of 26.1 µg with one ENV515-3-2 implant per eye (n=5 to 10) and 52.2 µg with two ENV515-3-2 implants per eye (n=10). Cohort 3 of the study will be conducted with 15 patients with bilateral open-angle glaucoma or ocular hypertension. ENV515-3-2 implants will be administered unilaterally in the study eye and followed for 12 months.

The ENV515-01 Phase 2a study design is informed by extensive prior clinical studies of ophthalmic travoprost formulations. US FDA approvals of two sterile ophthalmic topical formulations containing travoprost (TRAVATAN and TRAVATAN Z), and their subsequent clinical use have established travoprost's safety, tolerability, and IOP-lowering efficacy. The mechanism of action of travoprost has been postulated to occur via increasing of aqueous humor outflow through the uveoscleral pathway and potentially also via the TM. The topical administration of currently approved travoprost formulations likely results in only a small fraction of the total dose reaching the site of action due to the low efficiency of trans-corneal transport. Additionally, the conversion of the travoprost ester prodrug into its active acid form in the cornea and conjunctiva results in a high incidence of hyperemia for all topical PGA-based products. Compliance with the topical route of delivery of travoprost is generally perceived as low, thus contributing to more rapid progression of the disease and increased cost of treatment.

Due to the shortcomings of travoprost-based and, more broadly, PGA-based topical therapies, an extended release formulation delivering travoprost directly to the site of action is compelling. For ENV515, the intracameral route of delivery was chosen as it elutes travoprost more proximally to the site of action of the aqueous humor outflow via both TM and uveoscleral pathways. Additionally, in support of this route of delivery, Ocular pharmacokinetic studies with ENV515 in Beagle dogs demonstrated effective conversion of the travoprost ester prodrug into its active acid form in the anterior chamber. Furthermore, this route of delivery bypasses the primary transport of the drug through the cornea and conjunctiva and, consequently, creates the potential for reduced hyperemia. Lastly, the intracameral route of delivery has the potential for significant dose sparing: in preclinical studies in normotensive Beagle dogs dosed with 121.2 µg of travoprost/eye delivered via a single dose of ENV515-1, the full IOP treatment effect of ~30% change from baseline was demonstrated over an 8-month period. Based on previous studies in Beagle dogs, more than 400 µg of TRAVATAN or TRAVATAN Z/eye would be necessary to

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achieve a comparable treatment effect for the same period. This body of knowledge concerning ENV515 makes it a promising experimental therapy with the potential to improve IOP control and reduce treatment-related AEs in glaucoma patients.

The three implant sizes of ENV515 were selected to account for the anticipated best anatomical fit into the human iridocorneal angle. The dose range of travoprost proposed in the ENV515-01 Phase 2a clinical study was established based on pharmacodynamic studies in normotensive Beagle dogs. In these studies, a single dose of one ENV515-3 implant (12.5 µg of travoprost) demonstrated a submaximal IOP-lowering effect over a 7-month period and a single dose of three ENV515-1 implants (121.2 µg of travoprost) demonstrated a maximal IOP-lowering effect over an 8-month period, thus demonstrating significant dose-sparing potential vs. the topical travoprost formulations.

ENV515-1 and ENV515-3 have been evaluated in Good Laboratory Practice (GLP) compliant, single-dose, intracameral administration toxicity studies in Beagle dogs, using the intended clinical formulation composition covering the ranges of sizes and doses being studied in Cohorts 1, 2 and 3 of the ENV515-01 Phase 2a clinical study. ENV515-3 and its closely related, higher dose variant ENV515-3-2 are being advanced into Cohorts 2 and 3 of the ENV515-01 Phase 2a clinical study, respectively. Toxicity assessments for ENV515-1 and ENV515-3 are complete through 6 months following a single administration in GLP-compliant study that included a 12 month recovery period. Repeat-dose cohorts are currently being assessed to support repeat dose administration in the clinic in future studies. In the completed GLP toxicology studies, two, three, and six implants of each size were dosed/eye (27 to 82 µg of travoprost/eye for ENV515-3 and 84 to 252 µg of travoprost/eye for ENV515-1).

Overall, administration of 2, 3, or 6 ENV515-1 or ENV515-3 travoprost-eluting intracameral implants in the GLP toxicology studies was well tolerated in Beagle dogs for 28 days, resulting in mild ocular inflammation associated with the presence of implants in the anterior chamber as well as pharmacological effects consistent with travoprost in this test system. Additionally, two, three, and six ENV515-3 implants per eye were well tolerated for 6 months and the 12 month recovery period. The implants settled into the iridocorneal angle as the study progressed, although their location in the angle varied over time. At no point were implants observed floating in the anterior chamber. There was no effect on corneal thickness in any group. Ocular findings included conjunctival hyperemia, anterior chamber cells, corneal vessels and edema, and limited anterior synechiae. For ENV515-3, ophthalmic findings were generally very mild or not observed in the two and three implant groups, and a dose proportionality was observed in the incidence and severity as the dose escalated, with no adverse findings noted in any group. Findings included small areas of corneal opacity and small peripheral anterior synechiae at the location of the implants. Findings were localized to the implant location and were generally mild in nature, and generally resolved during the course of the study. Pupil miosis was observed in all eyes given active implants as expected in this species, and IOP was reduced approximately 30-40% compared with baseline in all groups, and remained below baseline values through Month 12. Microscopic findings included mild signs of inflammation and foreign body reaction surrounding the implants. ENV515-3 microscopic findings at Month 6 were generally mild in nature, particularly in the two and three implant groups, and at Month 12 only small anterior

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synechiae persisted. Overall findings observed were noted at an increased incidence and severity for the larger ENV515-1 implant. Overall findings for ENV515-3 were mild and were often similar between placebo and high dose, indicating that the number, size, and shape of implants may impact tolerability of ENV515.

Aqueous humor exposure to travoprost acid peaked on Day 3 for ENV515-1 and Month 6 for ENV515-3, and ocular tissue exposure was highest in cornea and iris/ciliary body, with minimal exposure in the conjunctiva, and was highest at Day 28 for ENV515-1 and at Month 6 for ENV515-3.

There was no observable systemic toxicity at any dose in the Beagle dogs as determined by clinical signs, body weight, food consumption, clinical pathology, and necropsy observations. Systemic exposure to ENV515 was very low following intracameral administration in Beagle dogs; plasma travoprost levels were detectable above the lower limit of quantitation in the high-dose animals generally only at the earliest time points evaluated (30 minutes post-dose), and was lower than the levels demonstrated for topical TRAVATAN Z.

The No Observed Adverse Effect Level (NOAEL) for 28 days in Beagle dogs was 6 ENV515-1 implants per eye (252.0 µg travoprost per eye) and 6 ENV515-3 implants per eye (82.2 µg travoprost per eye). The NOAEL for ENV515-3 for 6 months in Beagle dogs was 6 ENV515-3 implants per eye (82.2 µg travoprost/eye).

The dose levels of travoprost in Cohort 1 of this clinical study, administered via single, unilateral intracameral injection of ENV515-1 and ENV515-3 formulations, were 28.2 µg/eye, 42.3 µg/eye, 42.5 µg/eye, and 85.0 µg/eye. The four dose levels were achieved via the following combinations of numbers and sizes of implants: 28.2 µg (two ENV515-3 implants), 42.3 µg (three ENV515-3 implants), 42.5 µg (one ENV515-1 implant), and 85.0 µg (two ENV515-1 implants). The single, unilateral dose of travoprost dosed in Cohort 2 of this clinical study, administered via intracameral injection was two ENV515-3 implants/eye. The proposed single, unilateral dose levels of travoprost in Cohort 3 of this clinical study, administered via intracameral injection, consist of one or two ENV515-3-2 implants/eye, with approximately 26.1 µg of travoprost/eye or 52.2 µg travoprost/eye for the low and high doses, respectively.

Overall, the body of evidence suggests that with careful clinical ophthalmic monitoring and intracameral injection technique, the risk of potential serious adverse events (SAEs) in this Phase 2a study is low. Patients in this trial will be carefully monitored by a comprehensive set of ophthalmic evaluations. The exposure to the intracameral implant is limited by its prospectively scheduled implant removal on Day 28 in Cohort 1 of the study and the option to remove the implant in Cohorts 2 and 3.

1.4. Summary of Results from Cohort 1 of ENV515-01 Phase 2a Study

1.4.1. Summary of Disposition of Cohort 1 Patients in ENV515-01 Phase 2a Study

Patient disposition is presented in [Table 9](#). A total of 21 patients were enrolled and randomized into Cohort 1 across 10 sites. During the early enrollment stage of the study, dosing of ENV515-1 larger size implant was discontinued due to suboptimal anatomical fit into

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the human iridocorneal angle resulting in transient peripheral corneal edema from contact with the implant. For this reason, only four patients were randomized and treated with ENV515-1 while 17 patients were randomized and treated with the smaller size ENV515-3 implant. All patients completed the study per protocol and there were no early discontinuations from the study.

Table 9: Patient Disposition Table for Cohort 1 of ENV515-01 Phase 2a Study

	ENV515-3		ENV515-1		All Groups
	Group 1 (low dose) n (%)	Group 2 (high dose) n (%)	Group 3 (low dose) n (%)	Group 4 (high dose) n (%)	All Groups n (%)
Randomized	7 (100)	10 (100)	2 (100)	2 (100)	21 (100)
Treated	7 (100)	10 (100)	2 (100)	2 (100)	21 (100)
Analysis Populations					
Safety	7 (100)	10 (100)	2 (100)	2 (100)	21 (100)
Intent-to-treat	7 (100)	10 (100)	2 (100)	2 (100)	21 (100)
Per-protocol	7 (100)	10 (100)	2 (100)	2 (100)	21 (100)
Study Completion					
Completed	7 (100)	10 (100)	2 (100)	2 (100)	21 (100)
Discontinued	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

1.4.2. Summary of Efficacy Results from Cohort 1 of ENV515-01 Phase 2a Study

In the Cohort 1 intent-to-treat population (ITT), mean decreases from baseline diurnal IOP at Day 25 of the study were observed in all 4 dose levels of ENV515 intracameral travoprost studied in 21 patients with bilateral open-angle glaucoma or ocular hypertension who were scheduled for upcoming cataract surgery in a single eye (the study eye, p-values < 0.05 for all dose groups). In general, less robust response was observed in the eyes treated with the ENV515-1 larger size implants in comparison with the response observed in the ENV515-3 smaller sized implants. For the non-study eyes dosed with TRAVATAN Z, the IOP-lowering treatment effect was comparable to the high dose of ENV515-3. ENV515-1 dosing was discontinued in the early portion of the study and only low dose of the ENV515-3 formulation is progressed into Cohort 2

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of the study. Results of these analyses in the per-protocol population were identical to those in the ITT population.

ENV515-3 change from baseline in average diurnal IOP at Day 25 ITT (14.2.1.1, p 9 of tables):

- Low dose (28.2 µg travoprost, 2 implants/eye): -5.1 ± 1.7 mmHg or $-21.3 \pm 8.3\%$ (mean \pm SD, n=7, p < 0.001)
- High dose (42.3 µg travoprost, 3 implants/eye): -6.7 ± 2.1 mmHg or $-27.9 \pm 9.1\%$ (mean \pm SD, n=10, p < 0.001)

ENV515-1 change from baseline in average diurnal IOP at Day 25 ITT (14.2.1.1, p 9 of tables):

- Low dose (42.5 µg travoprost, 1 implants/eye): -3.2 ± 1.2 mmHg or $-12.6 \pm 3.2\%$ (mean \pm SD, n=7, p < 0.025)
- High dose (85 µg travoprost, 3 implants/eye): -5.7 ± 0.7 mmHg or $-21.3 \pm 1.1\%$ (mean \pm SD, n=10, p < 0.001)

TRAVATAN Z change from baseline in average diurnal IOP at Day 25 ITT (14.2.1.1, p 9 of tables):

- -6.6 ± 1.8 mmHg or $-28.0 \pm 7.7\%$ (mean \pm SD, n=21, p < 0.001)

1.4.3. Summary of Safety Results from Cohort 1 of ENV515-01 Phase 2a Study

There was no systemic exposure to travoprost based on systemic PK study and none of the non-ocular adverse events were suspected to be related to the ENV515 (e.g. hernia, oral herpes, and pulled hamstring). The ocular adverse events observed in the study were generally mild in nature, occurring mostly early in the study (Table 10). The majority of the adverse events were related to the dosing procedure which involved intracameral injection of ENV515 (Table 11). In one patient, a late occurring case of inferior peripheral corneal edema was observed and attributed to a narrow iridocorneal angle via anterior chamber OCT ($AOD_{SL} = 126 \mu\text{m}$). The implant was seen to be contact with the peripheral cornea by gonioscopy at the time of the edema. The patient was initially classified as having open angle based on gonioscopy evaluation (Table 11). For that reason, anterior chamber OCT-based angle evaluation is used as inclusion criteria for Cohort 2. During the early enrollment stage of the study, dosing of the ENV515-1 larger size implant was discontinued due to suboptimal anatomical fit into the human iridocorneal angle and high incidence of mild, transient AEs (Table 10)

One patient in the high dose arm of ENV515-3 (three implants/eye) experienced a SAE related to decrease in corneal endothelial cell count, with one additional patient in this dose arm experiencing a decrease in corneal endothelial cell count greater than 10% change from baseline, which was not classified as an AE. There were no other adverse events associated with the decrease in corneal endothelial cell count in these two patients, including no changes in corneal thickness or BCVA. No impact on corneal endothelium was observed in the low dose arm of ENV515-3 (two implants/eye) nor in the two dose arms of the larger sized ENV515-1 (one and two implants/eye, respectively). The observed decrease in the corneal endothelial cell counts was observed only in the three implants/eye dose group of ENV515-3 and was attributed to the third

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ENV515-3 implant extending out of the iridocorneal angle (in some cases, in a three implant vertical stack), as observed during gonioscopy exams. There was no evidence of progression of endothelial cell loss after explantation.

Table 10: Overall Summary of Adverse Events by Patient Classification

Category	ENV515-3		ENV515-1		TRAVATAN Z
	Group 1 (low dose) (n=7) n (%)	Group 2 (high dose) (n=10) n (%)	Group 3 (low dose) (n=2) n (%)	Group 4 (high dose) (n=2) n (%)	All Groups (non-study eye) (n=21) n (%)
At least 1 ocular AE	4 (57)	7 (70)	2 (100)	2 (100)	7 (33)
At least 1 ocular AE unresolved by last visit	0	2 (20)	0	0	0
At least 1 early ocular AE (Day 1-7)	4 (57)	7 (70)	2 (100)	2 (100)	3 (14)
At least 1 late ocular AE (Day 19-25)	0	1 (10)	1 (50)	0	2 (10)

Table 11: Classification of Adverse Events Occurring in > 1 Patient

Preferred Term	ENV515-3		ENV515-1		TRAVATAN Z
	Group 1 (low dose) (n=7) n (%)	Group 2 (high dose) (n=10) n (%)	Group 3 (low dose) (n=2) n (%)	Group 4 (high dose) (n=2) n (%)	All Groups (non-study eye) (n=21) n (%)
Ocular hyperemia	4 (57)	4 (40)	2 (100)	1 (50)	4 (19)
Foreign body sensation in eyes	1 (14)	3 (30)	2 (100)	1 (50)	0
Punctate keratitis	3 (43)	1 (10)	2 (100)	1 (50)	1 (5)
Anterior chamber cell	1 (14)	2 (20)	0	1 (50)	0

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	ENV515-3		ENV515-1		TRAVATAN Z
Conjunctival haemorrhage	1 (14)	3 (30)	0	0	1 (5)
Lacrimation increased	0	3 (30)	1 (50)	0	0
Iritis	0	2 (20)	0	1 (50)	0
Photophobia	0	2 (20)	0	1 (50)	1 (5)
Posterior capsule opacification	0	2 (20)*	0	0	0

*Occurred after cataract removal and intraocular lens (IOL) implantation

1.5. Interim Summary of Results from Cohort 2 of ENV515-01 Phase 2a Study

1.5.1. Summary of Disposition of Cohort 2 Patients in ENV515-01 Phase 2a Study

Patient disposition is presented in [Table 12](#). A total of five patients were enrolled into the study across two sites. All patients completed the study and there were no early discontinuations.

Table 12: Patient Disposition Table for Cohort 2 of ENV515-01 Phase 2a Study

	ENV515-3 (n=5)
Category	n (%)
Treated	5 (100)
Safety	5 (100)
Intent-to-treat	5 (100)
Per-protocol	4 (100)
Completed 3 months post dose	5 (100)
Discontinued	0 (0)

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1.5.2. Interim Summary of Safety Results from Cohort 2 of ENV515-01 Phase 2a Study

There were no SAEs reported in Cohort 2 of the study. The ocular adverse events observed in the study were generally mild in nature and related to the injection procedure. ([Table 13](#) and [Table 14](#)).

Table 13: Overall Summary of Ocular Adverse Events for ENV515-3 Excluding Hyperemia

Reported Events (summarized by preferred term)	Number of Subjects n (%)	Severity by AE incidence reported	Causality	Outcome
Foreign body sensation	4 (80)	3 -Mild 1 - Moderate	4 - Injection Procedure 1 - ENV515 Implant	Resolved
Endothelial cell count loss	2 (40)	Mild	ENV515 Implant	1 - Ongoing 1 - Resolved
Punctate keratitis	2 (40)	1 – Mild 1 - Moderate	1 - Injection Procedure 1 - Unrelated	Resolved
Blurred vision	2 (40)	Mild	1 - ENV515 Implant 1 - Unrelated	Resolved
Anterior chamber cell and flare	1 (20)	Mild	Injection Procedure	Resolved
Photophobia	1 (20)	Mild	Injection Procedure	Resolved
Iritis	1 (20)	Mild	Injection Procedure	Resolved
Corneal edema	1 (20)	Moderate and Mild	ENV515 Implant	Resolved
Focal microcystic epithelial edema	1 (20)	Mild	ENV515 Implant	Resolved
Trichiatic eyelash	1 (20)	Mild	Unrelated	Resolved

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Ocular soreness	1 (20)	Moderate	Injection Procedure	Resolved
Eyelid edema	1 (20)	Mild	Injection Procedure	Resolved
Ocular discomfort	1 (20)	1 – Mild 1 - Moderate	Injection Procedure and Unrelated	Resolved
Worsening of visual field	1 (20)	Mild	Unrelated	Ongoing

Table 14: Summary of Hyperemia Adverse Events for ENV515-3 Dose Arm

Reported Adverse Events	Number of Incidences Reported	Study Eye or Both Eyes	Severity	Causality	Outcome
Ocular hyperemia	2	Study Eye	Severe	Injection Procedure	Resolved
Ocular hyperemia	2	Study Eye	Moderate	Injection Procedure	Resolved
Ocular hyperemia	1	Study Eye	Moderate	ENV515 Implant	Resolved
Ocular hyperemia	10	8 – Study Eye 2 – Both Eyes	Mild	6 – Unrelated 4 – ENV515 Implant	Resolved
Conjunctival hyperemia	1	Study Eye	Moderate	Injection Procedure	Resolved

1.6. Summary of the Known and Potential Risks and Benefits to Human Patients

The potential AEs for human subjects receiving ENV515 may occur due to 1) the use of travoprost in general; 2) the intracameral injection procedure; 3) the use of a solid implant in the anterior chamber; 4) the use of the PLA biodegradable polymers used for the ENV515 extended release delivery system; 5) the combination of 1-4 above; and 6) any additional effects due to ENV515. Summary of relevant existing clinical data across these safety considerations provides a useful context for ENV515 clinical evaluation:

- There is extensive safety, tolerability, and efficacy information on the topical administration of travoprost in patients with ocular hypertension or open-angle glaucoma, based on the US FDA approval of TRAVATAN and TRAVATAN Z. The

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- most common AEs observed in controlled clinical studies with TRAVATAN and TRAVATAN Z are provided in more detail below.
- Extensive information has also been published on the safety and tolerability of intraocular injections, based on the intravitreal administration of LUCENTIS®, EYLEA®, and OZURDEX®, which are currently approved and marketed in the US. Examples of adverse reactions reported for intravitreal injections include IOP increase, conjunctival hemorrhage, eye pain, conjunctival hyperemia, ocular hypertension, cataract, vitreous detachment and headache (OZURDEX® package insert [6]). Intraocular infections, endophthalmitis, may also occur after intraocular injections.
 - Anterior chamber paracentesis is a common procedure for relief of IOP due to acute angle closure glaucoma.
 - In addition, there is safety and tolerability information of intracameral injection and solid implants localized in the anterior chamber based on, for example, the clinical development of SURODEX (7), an anterior chamber dexamethasone PLGA implant. Solid implants localized in the anterior chamber may cause loss of corneal endothelial cells, corneal edema, corneal opacities, and anterior chamber inflammation (flare, cells and iritis).
 - The safety and tolerability of intraocular use of biodegradable PLGA polymers are based on the intraocular use of OZURDEX and SURODEX, which are PLGA-based, extended release formulations of dexamethasone for intravitreal and intracameral injections, respectively.
 - The safety and tolerability information from the completed portions of Cohorts 1 and 2 of the study provides useful information for Cohort 3 (please see details in [Section 1.4](#)). The safety profile of ENV515 is related to the size and number of ENV515 implants administered per eye. The dose selected for Cohort 2 of this trial, two ENV515-3 implants per eye (28.2 µg of travoprost) was associated with only mild and transient adverse events related to the insertion procedure of ENV515: ocular hyperemia, foreign body sensation, punctate keratitis, anterior chamber cells and procedural pain ([Table 11](#) and [Table 14](#)). Larger number of ENV515-3 implants per eye administered in Cohort 1 (three implants/eye) resulted in loss of corneal endothelial cell count in two cases (without vision loss or increase in corneal thickness) with no progression after explantation ([Section 1.4.3](#)).

The most common adverse reaction observed in controlled clinical studies with TRAVATAN and TRAVATAN Z was ocular hyperemia which was reported in 30 to 50% of patients (TRAVATAN Z package insert [2]). Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity (VA), eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN or TRAVATAN Z included abnormal vision, blepharitis, blurred vision,

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cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing. Non-ocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infections. In post-marketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Travoprost ophthalmic solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment. Travoprost ophthalmic solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. Travoprost ophthalmic solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Topical travoprost has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

There are no adequate and well-controlled studies of TRAVATAN Z administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus. A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z is administered to a nursing woman. No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients. Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

The safety of the use of a solid implant in the anterior chamber may be informed by the current studies of minimally invasive glaucoma implants (MIGs). For the currently approved iStent® MIG product that is administered during cataract procedure, the most common post-operative AEs reported in the randomized pivotal trial included early post-operative corneal edema (8%), BCVA loss of = 1 line at or after the 3 month visit (7%), posterior capsular opacification (6%),

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stent obstruction (4%) early post-operative anterior chamber cells (3%), and early post-operative corneal abrasion (3%). Due to the potential for corneal touch, the potential for damage to the corneal endothelium is present.

Data from GLP toxicology and toxicokinetics studies of ENV515-1 and ENV515-3 in naïve male Beagle dogs demonstrate that up to six ENV515-1 and six ENV515-3 implants per eye were well tolerated in this model over 28 days and up to six ENV515-3 implants per eye were well tolerated in this model over six months. Animals (two to six per group per terminal time point) received a single administration of up to six implants per eye (252.0 µg per eye for ENV515-1 and 82.2 µg per eye for ENV515-3) and were followed for up to six or 12 (recovery) months. For ENV515-3, ophthalmic findings were generally very mild or not observed in the two and three implant groups, and a dose proportionality was observed in the incidence and severity as the dose escalated, with no adverse findings noted in the high dose group. Findings included small areas of corneal opacity and small peripheral anterior synechiae at the location of the implants. Findings were localized to the implant location and were generally mild in nature, and generally resolved during the course of the study. Pupil miosis and decreased IOP (30-40% decrease in IOP from baseline) were observed throughout the 28-day study period, and IOP remained below baseline in most groups through Months 6 or 12. Systemic exposure to travoprost was minimal ($C_{max} = 46$ pg/mL), aqueous humor exposure to travoprost acid peaked on Day 3 for ENV515-1 and Month 6 for ENV515-3, and ocular tissue exposure was highest in cornea and iris/ciliary body, with minimal exposure in the conjunctiva and was highest at Day 28 for ENV515-1 and at Month 6 for ENV515-3. Microscopic findings included mild signs of inflammation and foreign body reaction surrounding the implants. ENV515-3 microscopic findings at Month 6 were generally mild in nature, particularly in the two and three implant groups, and at Month 12 only small anterior synechiae persisted. Overall findings observed were noted at an increased incidence and severity for the larger ENV515-1 implant, were mild or not observed for ENV515-3, and were often similar between placebo and high dose, indicating that the number, size, and shape of implants may impact tolerability of ENV515. The NOAEL for 28 days in Beagle dogs was six ENV515-1 implants (252.0 µg travoprost per eye, 504.0 µg travoprost per animal) and six ENV515-3 implants (82.2 µg travoprost per eye, 164.4 µg travoprost per animal). The NOAEL for ENV515-3 for six months in Beagle dogs in this study was six ENV515-3 implants (82.2 µg travoprost/eye).

Based on the results from the ENV515 nonclinical studies and prior findings of safety and efficacy for topical travoprost for TRAVATAN and TRAVATAN Z, it is considered that there are no nonclinical ocular or systemic toxicity findings that preclude the use of ENV515 in humans as described in the completed Cohort 1, Cohort 2 and Cohort 3 phases of this clinical study.

There is no antidote for ENV515. However, in cases of suspected overdose or adverse safety events, ENV515 implants can be removed. For this reason, the Cohort 1 phase of ENV515-01 employed a novel clinical trial design implemented in glaucoma patients scheduled for cataract surgery. If suspected overdose or serious adverse safety event occur, the patient could have undergone the cataract procedure at an earlier date during which the ENV515 implants were removed through the corneal incision needed for the cataract removal in Cohort 1. A similar

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implant removal procedure can be used for implant removal in the Cohort 2 and 3 phases of the study, which would require a standalone clear corneal incision.

1.7. GCP Compliance

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization (ICH), Good Clinical Practice (GCP) guidelines, Code of Federal Regulations Title 21 and other applicable guidelines and regulatory requirements.

1.8. Population to Be Studied

The Cohort 1 study population included 21 patients between 18 and 85 years of age with a diagnosis of bilateral ocular hypertension or early primary open-angle glaucoma with the need for cataract removal and intraocular lens implantation.

The Cohort 2 study population included 5 patients and Cohort 3 includes 15 patients between 18 and 85 years of age with a diagnosis of bilateral ocular hypertension or early primary open-angle glaucoma.

The patients for all phases have been enrolled at centers across the United States in this Phase 2a trial with ENV515 (travoprost) Intracameral Implants.

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2. TRIAL OBJECTIVES AND PURPOSE, COHORT 1

The primary objectives of the Cohort 1 phase of this study were to:

- Evaluate the safety and tolerability of ENV515 (travoprost) Intracameral Implants in patients with bilateral ocular hypertension or early primary open-angle glaucoma; and
- Evaluate the efficacy of ENV515 (travoprost) Intracameral Implants in lowering IOP in patients with bilateral ocular hypertension or early primary open-angle glaucoma.

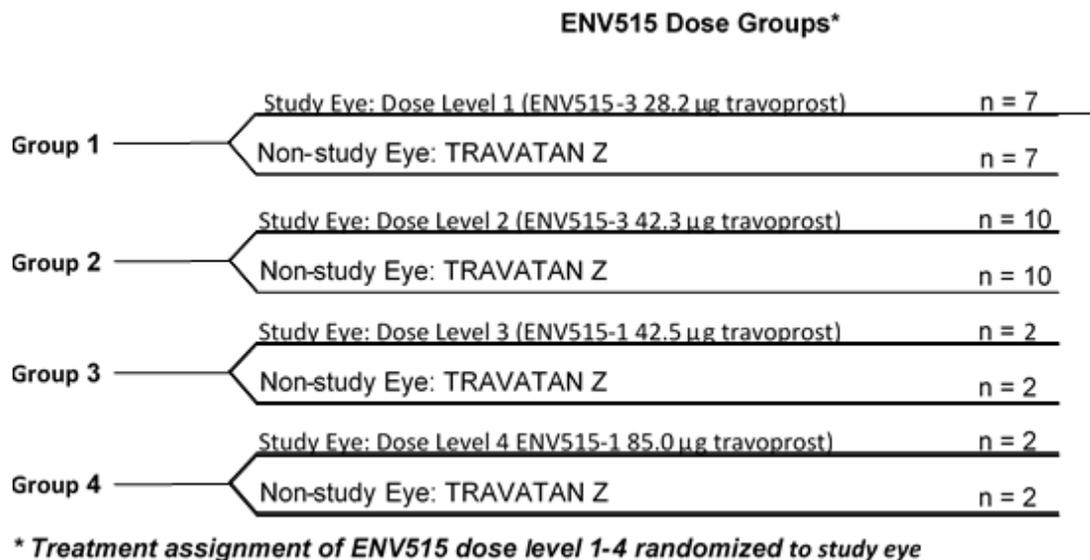
The secondary objectives of the Cohort 1 phase of this study were to:

- Determine the PK levels of travoprost in the aqueous humor at the time of the cataract surgery (4 weeks post-implantation);
- Determine the systemic exposure (levels of travoprost in plasma); and
- Determine the residual level of travoprost in the implant removed at the time of the cataract surgery (4 weeks post-implantation).

3. TRIAL DESIGN, COHORT 1

The Cohort 1 phase of this study was a multicenter, randomized, open-label, parallel-group, dose-ranging, 28-day Phase 2a trial to assess the safety, tolerability, efficacy, aqueous humor PK, systemic exposure, and remaining travoprost in ENV515 implants for 4 dose levels of ENV515, and was conducted in 21 patients with bilateral open-angle glaucoma or ocular hypertension (see inclusion criteria in [Section 4.1](#)) who are scheduled for upcoming cataract surgery in a single eye. For the purposes of the Cohort 1 phase of this study, early primary open-angle glaucoma was defined as focal non-full thickness rim thinning with no VF changes or small isolated nasal step or paracentral scotoma or Seidel's scotoma with VF mean defect (MD) of MD \leq -8.0. The dose levels of travoprost in the Cohort 1 phase of this clinical study, administered via single, unilateral intracameral injection of ENV515-1 and ENV515-3 formulations, were 28.2 $\mu\text{g}/\text{eye}$, 42.3 $\mu\text{g}/\text{eye}$, 42.5 $\mu\text{g}/\text{eye}$ and 85.0 $\mu\text{g}/\text{eye}$. The 4 dose level groups were achieved via the following numbers and sizes of implants: 28.2 μg (2 ENV515-3 implants), 42.3 μg (3 ENV515-3 implants), 42.5 μg (1 ENV515-1 implant), and 85.0 μg (2 ENV515-1 implants). ENV515 implants were administered unilaterally in the study eye (pre-surgical eye) 4 weeks prior to the cataract surgery and the implants were retrieved during the cataract surgery. All non-study eyes received open label TRAVATAN Z (travoprost ophthalmic solution), 0.004% per their usual treatment regimen ([Figure 2](#)).

Figure 2: ENV515 Treatment Arms, Cohort 1



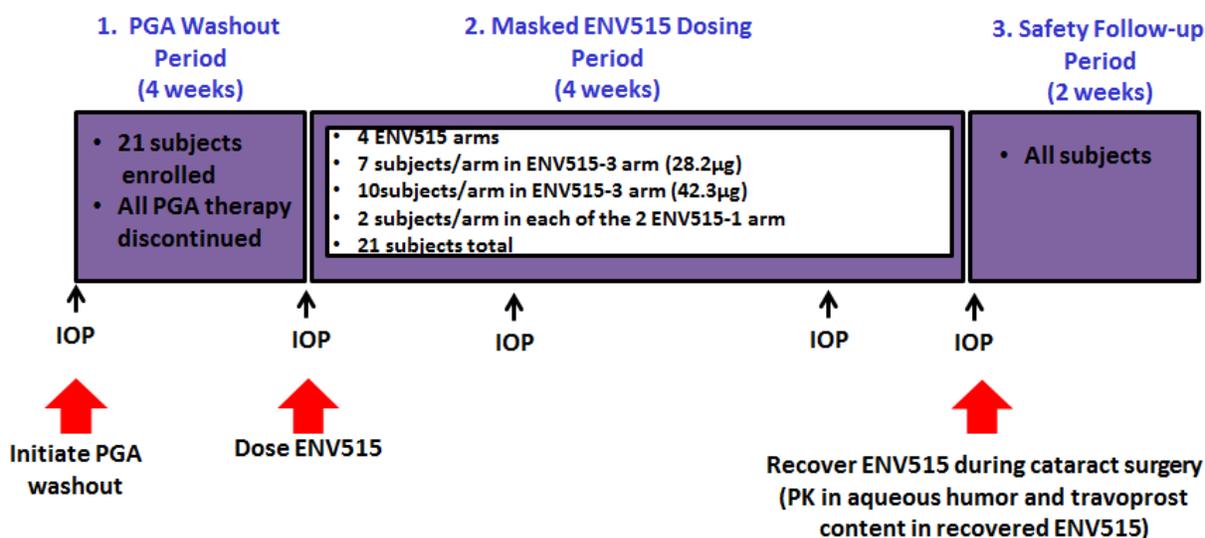
The four ENV515 dose levels were administered in a parallel group design, with each patient participating in only one group. Following Day 25 of the treatment phase (Visit 3/Day 1 to Visit 8/Day 25 [± 1 day]), analysis of IOP treatment effect at Visit 8/Day 25 (± 1 day) as % change in diurnal IOP from diurnal IOP baseline was conducted as the primary efficacy outcome measure. Following the completion of the study follow-up (Visit 11/Day 42 to Day 49), all safety and tolerability assessments were conducted. The assessment of safety and tolerability

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included, but was not be limited to, data from the AE reports, corneal thickness, endothelial cell morphology, endothelial cell counts, and slit lamp examination.

The study design included 11 clinic visits over approximately 10 to 12 weeks depending on the duration of the variable length screening and follow-up periods. During the Screening Visit (Visit 1/Day -35 to -28), patients were required to washout current glaucoma medication(s) if currently using them (Section 16). Patients were required to return for an IOP baseline check during the Baseline Visit (Visit 2/Day -7 to -1) following the wash-out period. Once randomized, a single dose of ENV515 was given via intracameral injection during Visit 3/Day 1 (Figure 3).

Figure 3: Study Design for ENV515-01 (Cohort 1): 4-Week Phase 2a Safety, Tolerability, and IOP Lowering Effects of ENV515 in Glaucoma Patients in Need of Cataract Surgery



Patients received the assigned dose of ENV515 in the pre-surgical eye on Day 1 and received TRAVATAN Z drops to use in the non-study eye once daily (8 p.m. \pm 1 hour) from Day 1 to Day 25. ENV515 implants were scheduled for removal at Visit 9/Day 28 before cataract removal.

Diurnal IOP curves were measured during two visits (Visit 2/Day -7 to -1 and Visit 8/Day 25 \pm 1 day). During these visits, study patients were expected to remain in the clinic from 8:00 a.m. to 5:00 p.m. However, at the discretion of the investigator, patients will be permitted to leave the clinic between measurements for a specified period of time outlined by visit in Section 5.2 and Section 5.8.

Throughout the study, patients underwent multiple safety assessments. A schedule of assessments is outlined in the sections below and summarized in Table 1.

3.1. Safety Evaluations, Cohort 1

3.1.1. Review of Safety Data by Medical Monitor, Cohort 1

A review of unmasked ocular safety data from each patient were performed on an ongoing basis by a medical monitor or Envisia designee. All ocular safety data for each patient was provided to the medical monitor as it was generated throughout the trial. A patient could be discontinued at any time during the study at the discretion of the medical monitor for reasons referenced in, but not limited to, [Section 4.4](#). Assessment of safety and tolerability included, but was not be limited to, AE reports, corneal thickness, endothelial cell morphology, endothelial cell counts, and slit lamp examination. In addition, a meeting with the Envisia project team might be requested by the medical monitor at any time during the study to conduct a full evaluation of safety, which may have resulted in a recommendation to terminate the study.

3.2. Endpoints, Cohort 1

The endpoints of the Cohort 1 phase of this study were:

- Incidence of AEs;
- Changes in ophthalmic examination parameters (slit-lamp biomicroscopy, corneal staining, dilated funduscopy exam, anterior segment photos, pupil measurement, ocular symptom questionnaire, and VF as measured by the Humphrey Field Analyzer using program 24-2);
- Changes in endothelial cell count and endothelial cell morphology using specular microscopy;
- Changes in corneal thickness as measured using pachymetry;
- Changes in IOP, including diurnal curve, as measured using a Goldmann applanation tonometer;
- Changes in VA with manifest refraction using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart;
- Changes in physical examination, vital signs, and laboratory parameters;
- Rate of discontinuation from the study;
- Drug levels (travoprost ester and travoprost free acid) in aqueous humor collected during cataract removal;
- Drug levels (travoprost free acid) in plasma; and
- Residual amount of travoprost (combined ester and free acid) remaining in the implants recovered during cataract surgery.

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3.2.1. Trial Treatments, Cohort 1

The 4 ENV515 dose levels were administered in a parallel group design, with each patient participating in only one group. The 4 dose levels were achieved via the following numbers and sizes of implants: 28.2 µg (two ENV515-3 implants), 42.3 µg (three ENV515-3 implants), 42.5 µg (one ENV515-1 implant), and 85.0 µg (two ENV515-1 implants). Two patients per dose in the two ENV515-1 dose groups, 5 patients per dose in the 2 implants/eye ENV515-3 dose group and 11 patients per dose in the 3 implants/eye ENV515-3 dose group had the active dose assigned to the pre-surgical eye that was scheduled for cataract removal, with the non-study eye receiving TRAVATAN Z once daily per package insert from Day 1 through Day 25.

3.3. Methods to Minimize Bias in Cohort 1

To minimize bias, patients were assigned to 1 of the 4 dose levels of ENV515 within each investigative site. The non-study eye will receive TRAVATAN Z.

The randomization code for this study was generated by Envisia or its designee. The patients, investigators, site staff, and project teams at Envisia, the medical monitor, and the CRO were unmasked to treatment assignment.

4. SELECTION AND WITHDRAWAL OF PATIENTS, COHORT 1

4.1. Patient Inclusion Criteria, Cohort 1

Individuals of either gender or any race were eligible for participation in Cohort 1 if they:

1. Provide written informed consent prior to study procedures.
2. Are between 18 and 85 years of age.
3. Have a willingness to comply with the investigator's instructions, attend study visits, and stop prior eye medications to treat glaucoma and/or ocular hypertension.
4. If female, patient must be non-pregnant and non-lactating, and those of childbearing potential must be using an acceptable method of birth control (i.e., an intrauterine contraceptive device with a failure rate of <1%, hormonal contraceptives, or a barrier method). If a female patient is abstinent, she must agree to use one of the acceptable methods if she becomes sexually active.
5. Have a diagnosis of bilateral ocular hypertension or mild to moderate primary open-angle glaucoma and have open normal appearing anterior chamber angles (Shaffer classification Grade 3 or 4, angle of approach 20° or larger).
6. Are currently treated with topical PGA for ocular hypertension.
7. At the Baseline Visit after washout (Visit 2), have IOP measurements that meet all of the following:
 - a. Have an IOP at 8:00 a.m. (± 30 minutes) and at 10:00 a.m. (± 30 minutes) between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes
 - b. Have an IOP at 4:00 p.m. (± 30 minutes) between 19-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye
8. Have an IOP ≤ 34 mm Hg in each eye at all other time points prior to the Baseline Visit (Visit 2).
9. At the Screening Visit (Visit 1), have an IOP in both eyes that is considered to be safe, so that clinical stability of vision and the optic nerve is likely throughout the trial.
10. Have endothelial cell counts of at least 2000 cells/mm² and normal endothelial cell morphology at the Screening Visit (Visit 1) as evaluated by central reading center.
11. Patient is a candidate for and has been scheduled for cataract extraction in a single eye within 60 days of Visit 1*.

* Following cataract removal, the patient may undergo additional procedures (e.g., iStent insertion).

4.2. Patient Exclusion Criteria, Cohort 1

Individuals are not eligible for study participation in Cohort 1 if they:

1. Are currently diagnosed with closed angle glaucoma, exfoliation syndrome or exfoliation glaucoma, and pigment dispersion or secondary glaucoma.
2. Have a history of glaucoma-related surgery (trabeculectomy, cryotherapy, laser iridotomy, etc.).
3. Have had intraocular conventional surgery, intraocular laser surgery, corneal refractive surgery or eyelids surgery within the past 3 months.
4. Are currently diagnosed with active infectious/noninfectious conjunctivitis, keratitis, uveitis, or moderate to severe blepharitis in either eye. (Chronic mild blepharitis or injection related to mild blepharitis, lid lag, mild dry eye or seasonal allergies are allowed.)
5. Are currently taking or have taken corticosteroids (oral, ocular, injectable, IV and/or topical) or used dermatology formulations of steroids in the vicinity of eyes in the 1 month prior to Visit 1 with the exception of inhaled, intranasal, or topical (dermal) steroids if on a stable dose; or have a history of chronic ocular corticosteroid (topical or intraocular) use within the past year.
6. Have a requirement for any ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Visit 2.
7. Have a history of recurrent corneal erosion syndrome, multiple corneal abrasions, or an abrasion that was slow to heal.
8. Have severe glaucoma with a mean defect (MD) worse than -8.0, central island of vision, or otherwise severe glaucoma that would not tolerate a possible short-term increase in IOP.
9. According to the investigator's best judgment, are at risk for progression of glaucoma, VF or VA worsening as a consequence of participation in the trial.
10. Have any abnormality preventing reliable applanation tonometry in either eye.
11. Have any corneal opacity or are uncooperative in such a way that restricts adequate examination of the ocular fundus or anterior chamber in either eye.
12. Are unwilling to discontinue use of contact lenses at least 2 days prior to Visit 2 for soft lenses and at least 7 days prior to Visit 2 for rigid gas permeable (RGP) lenses through completion of the study at Visit 11.
13. Have progressive retinal or optic nerve disease apart from glaucoma.
14. Have any clinically significant, serious, or severe medical or psychiatric condition.

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15. Are, in the opinion of the investigator, unable or unwilling to comply with study procedures, including attending the scheduled study visits.
16. Have a history, or a suspected history of drug or alcohol dependence in the preceding year.
17. Are unwilling to limit alcohol ingestion and smoking for the 8-hour period prior to and during study appointments after Visit 1.
18. Have received any investigational product within the past 30 days prior to Visit 1.
19. Have any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial such as travoprost or PLA excipients.
20. Have a history of insufficient response to PGA topical treatment, i.e., are PGA non-responders.
21. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same.
22. Have a central corneal thickness greater than 600 micrometers as determined by pachymetry at the Baseline Visit (Visit 2).
23. Had prior intraocular surgery or any ocular or systemic condition that may confound the study outcome per the investigator's recommendation.

4.3. Randomization Criteria, Cohort 1

At the Randomization Visit (Visit 3/Day 1), an eligible patient must:

- Continue to meet all inclusion/exclusion criteria as defined in [Sections 4.1](#) and [4.2](#)

4.4. Patient Withdrawal Criteria, Cohort 1

Any patient who wished to withdraw from the study on his or her own accord for any reason was entitled to do so without obligation. Patients who were withdrawn from the study prior to randomization could be replaced. Any patient could be removed from the study by the investigator if it is deemed necessary for the patient's safety.

In the event that withdrawal of a randomized patient was medically necessary or requested by the patient, the investigator made every attempt to complete all protocol safety assessments and visits through the cataract surgery combined with the removal of the ENV515 implant(s), and the post-surgery follow-up visits.

If patient withdrawal was required due to an AE or SAE, the cataract surgery combined with the removal of the ENV515 implant(s) should have occurred as soon as possible based on the judgment of the investigator and safety of the patient.

If an AE or SAE was unresolved at the time of the patient's final study visit, an effort was made to follow the patient until the AE or SAE is resolved or stabilized ([Section 17](#)), the patient was

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lost to follow-up, or there was some other resolution of the event. The investigator should have made every attempt to follow all SAEs to resolution.

4.4.1. Specific Withdrawal Criteria, Cohort 1

Following ongoing review of the data by the medical monitor, any individual patient safety concerns was discussed between the medical monitor and investigator. If the investigator determined that a patient should be discontinued and withdrawn from the study, the cataract surgery and removal of the ENV515 implant(s) should occur as soon as possible based on the judgment of the investigator. Any rescue therapy or procedures should be applied based on the judgment of the investigator.

A patient may be discontinued and withdrawn from the study at any time at the discretion of the investigator for any safety reason, including but not limited to those listed below:

- IOP measurement of 35 mm Hg or greater in either eye at any measurement
- Any clinically significant pole changes, including but not limited to:
 - Cystoid macular edema (CME)
 - Retinal pigment epithelium (RPE)
 - Disc rim pallor
- Pachymetry measurement of the central corneal thickness which reveals a change that falls outside of the normal variability when compared to the baseline measurement
 - An acute increase of 15% or greater in corneal thickness for a period of <24 hours after the instillation of study drug
 - A chronic increase of 10% or greater in corneal thickness for a period of >24 hours after the instillation of study drug
- A >10% decrease in central endothelial cell density as evaluated by the centralized reading center

In the event that study discontinuation and withdrawal of a randomized patient is necessary, the investigator should make every attempt to complete all protocol safety assessments and visits through the cataract surgery combined with the removal of the ENV515 implant(s), and the post-surgery follow-up visits. The cataract surgery combined with the removal of the ENV515 implant(s) should occur as soon as possible based on the judgment of the investigator. Unless the consent has been withdrawn, any patient is considered to be in the treatment phase of the study until the cataract surgery combined with ENV515 implant removal has been completed, and such patients should continue to be followed and will be expected to complete all pre- and post-surgery safety assessments and visits.

5. PROCEDURE SCHEDULE BY VISIT, COHORT 1

5.1. Visit 1/-35 to -28 days/Screening Evaluation, Cohort 1

At Visit 1, patients will be screened, and if eligible, enrolled into the study. Before any study specific assessments are performed, written informed consent will be obtained from each patient. During the visit, the procedures described below will be performed.

5.1.1. Screening Assessments, Cohort 1

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Obtain written informed consent
2. Obtain medical history, ocular history, and demographics (can be performed anytime during the site visit and does not need to follow the order as written)
3. Evaluate and record patient's medication usage (including concomitant medications taken within the past 30 days) (can be performed anytime during the site visit and does not need to follow the order as written)
4. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
5. Perform pupil measurement
6. Perform slit lamp biomicroscopy
7. Perform corneal staining
8. Measure IOP
9. Perform gonioscopy
10. Perform pachymetry (contact)
11. Perform specular microscopy (non-contact)
 - Non-contact specular microscopy can be performed anytime during the clinic visit and does not need to follow the order as written.
12. Assess VF
13. Perform anterior chamber OCT
14. Perform dilated funduscopy exam
15. Perform physical examination (can be performed anytime during the site visit and does not need to follow the order as written)

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16. Assess vital signs (can be performed anytime during the site visit and does not need to follow the order as written)
17. Collect non-fasting blood and urine for clinical laboratory tests
18. If female of childbearing potential, perform urine or serum pregnancy test
19. Verify that patient meets all applicable entry criteria
20. Query patient about whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

At the end of the examination, patients will be asked to discontinue their current glaucoma medication(s). [Section 16.2.2](#) references the duration of the washout period given different types of topical glaucoma therapy. The patient will be asked to return for the baseline visit after 4 weeks. The washout period may be extended up to 2 weeks, if it remains safe for the patient, to accommodate the patient's or the investigator's schedule.

5.1.2. Patient Instructions, Cohort 1

Before patients leave the clinic, they should receive an appointment for their next study visit and the following instructions:

- Discontinue use of all eye drop medications until the end of the study (if appropriate). With your doctor's approval, you may be able to use artificial tear eye drops.
- Remember not to use alcohol or tobacco products within 8 hours of your next clinic visit.
- At Visits 2 and 8, be prepared for a long clinic visit. You will be expected to have IOP measurements at 8:00 a.m., 10:00 a.m., and 4:00 p.m. You may leave the clinic after the 10:00 a.m. assessments, with your doctor's approval.
- Call your study site if you have any problems.
- Remember not to wear contact lenses 2 days for soft contact lenses and 7 days for RGP lenses prior to next visit

5.2. Visit 2/Day -7 to -1/Baseline, Cohort 1

Patients will be queried about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

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5.2.1. Baseline Assessments, Cohort 1

Assessments will be conducted in the following general order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction, the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes)
 - IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 8:00 a.m. (± 30 minutes)
6. Perform gonioscopy
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact)
 - Non-contact specular microscopy can be performed anytime during the site visit and does not need to follow the order as written.
9. Perform anterior chamber OCT
10. Perform physical examination (can be performed anytime during the site visit and does not need to follow the order as written)
11. Assess vital signs (can be performed anytime during the site visit and does not need to follow the order as written)
12. Collect non-fasting blood and urine for clinical laboratory tests
13. If female of childbearing potential, perform urine or serum pregnancy test
14. Measure IOP at 10:00 a.m. (± 30 minutes)
 - IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 10:00 a.m. (± 30 minutes)
15. Measure IOP at 4:00 p.m. (± 30 minutes)
 - IOP must be between 19-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 4:00 p.m. (± 30 minutes)
16. Perform dilated fundoscopic examination
17. Verify that patient meets all entry criteria

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Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

5.2.2. Patient Instructions, Cohort 1

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.1.2](#).

5.3. Visit 3/Day 1/Randomization/Treatment, Cohort 1

Query patient about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

5.3.1. Pre-dose Assessments, Cohort 1

Assessments will be conducted in the following general order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes)
5. Instill one drop of VIGAMOX into the study eye
6. If female of childbearing potential, perform urine or serum pregnancy test
7. Verify that patient meets all entry criteria

5.3.2. Randomization and Study Drug Administration, Cohort 1

Patients will be assessed to ensure they still qualify to participate in the study based on the inclusion/exclusion criteria and randomization criteria ([Section 4.3](#)). The study principal investigator will administer the first and only dose of study medication into the pre-surgical study eye (see [Section 6.1.1](#). Implantation of ENV515). The ENV515 experimental medication will be delivered at 10:00 a.m. (± 30 minutes). TRAVATAN Z will be administered into the non-study eye by the patient at 8 p.m. (± 30 minutes).

At the randomization/treatment visit (Visit 3), the patient's pre-surgical eye will be randomly assigned to 1 of the 4 dose levels of ENV515 and patients will receive 1 to 3 ENV515 (travoprost) Intracameral Implant(s) into the pre-surgical eye via intracameral injection

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administered via the provided intracameral implant applicator. The site will receive randomization information based on randomization schedule following Visit 2 specifying which ENV515 formulation (ENV515-1 or ENV515-3) and how many implants to administer. The randomization code for this open-label study will be computer-generated prior to the study start. To randomize a patient (Visit 3), the investigator (or designee) will confirm in the electronic Case Report Form (eCRF) that the patient remains qualified for the study. The eCRF will automatically assign the dose and number of implants that the patient should receive based on a prospectively prepared computer generated code list.

5.3.3. Post-dose Assessments, Cohort 1

1. Perform slit lamp biomicroscopy
2. Dispense TRAVATAN Z to the patient

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~12:00 p.m.); however, at the discretion of the investigator, patients will be permitted to leave the clinic following the completion of the dosing.

5.3.4. Patient Instructions, Cohort 1

Before patients leave the clinic, they should receive an appointment for their next study visit and the following instructions:

- Remember to use TRAVATAN Z once daily in the evening (as close to 8:00 p.m. as you can) in the eye that is NOT having cataract surgery. DO NOT PUT TRAVATAN Z in the eye that had the ENV515 implant(s). Continue using TRAVATAN Z only through Day 24, one day prior to Visit 8 (Day 25 ± 1 day). Please remember to bring TRAVATAN Z with you to Visit 8 (Day 25 ± 1 day) so that it can be collected from you.
- Continue to withhold (not use) all your other eye drop medications until the end of the study (if appropriate). With your doctor's approval, you may be able to use artificial tear eye drops.
- Remember not to use alcohol or tobacco products within 8 hours of your next clinic visit.
- Call your study site if you have any problems.
- Please avoid physical activities associated with jarring physical motions, such as horseback riding, for the rest of the study.

5.4. Visit 4/Day 3 ± 1 Day/Treatment Period, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

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Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes)
5. Perform gonioscopy
6. Perform anterior chamber OCT

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~10:00 a.m.). Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.3.4](#).

5.5. Visit 5/Day 7 \pm 1 Day/Treatment Period, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes)

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~9:00 a.m.). Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.1.2](#).

5.6. Visit 6/Day 14 \pm 1 Day/Treatment Period, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

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Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes)
6. Perform gonioscopy
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact)
 - Non-contact specular microscopy can be performed anytime during the site visit and does not need to follow the order as written.
9. Perform anterior chamber OCT
10. Perform dilated funduscopy exam
11. Collect non-fasting blood and urine for clinical laboratory tests and systemic PK

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~10:00 a.m.). Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.3.4](#).

5.7. Visit 7/Day 21 \pm 1 Day/Treatment Period, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform slit lamp biomicroscopy
3. Perform corneal staining

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4. Measure IOP at 8:00 a.m. (± 30 minutes)
5. Perform gonioscopy

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~10:00 a.m.). Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.3.4](#).

5.8. Visit 8/Day 25 \pm 1 Day/Treatment Period, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented. Collect TRAVATAN Z from the patient.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes)
6. Perform gonioscopy
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact)
 - Non-contact specular microscopy can be performed anytime during the site visit and does not need to follow the order as written.
9. Perform anterior chamber OCT
10. Measure IOP at 10:00 a.m. (± 30 minutes)
11. Measure IOP at 4:00 p.m. (± 30 minutes)
12. Perform dilated funduscopy examination
13. Collect TRAVATAN Z from the study patients

5.8.1. Disbursement and First Administration of Pre-Surgical Medications

Following the completion of all assessments, the patients will receive their pre-surgical anti-inflammatory and antibiotic medications: PRED FORTE, PROLENSA, and VIGAMOX. The

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medications will be administered by the patients on Day 26, 27, and 28 twice a day for each medication, once in the morning and once in the evening. Following the removal of the ENV515 implant (Visit 9/Day 28), it is upon the discretion of the investigator to determine the post-operative medication regimen. Patients will be provided with instructions on use of these medications and what to do to prepare for their cataract surgery.

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~4:30 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to 4:00 p.m. Before patients leave the clinic for the day, they should receive an appointment for their next study visit and the instructions provided in [Section 5.1.2](#).

5.9. Visit 9/Day 28/Cataract Surgery, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

5.9.1. Pre-surgery Assessment, Cohort 1

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes)
6. Perform gonioscopy to identify the location of the ENV515 implants to facilitate implant recovery during the cataract removal procedure
7. Additional assessment needed prior to cataract removal conducted per discretion of the principal investigator

5.9.2. Cataract Removal Procedure Combined with Aqueous Humor Sampling and Implant Recovery, Cohort 1

The cataract surgery and IOL implantation will be conducted according to the discretion of the principal investigator per established protocols. The following study-specific procedures will be performed during the cataract surgery:

1. The implant location(s) are identified by gonioscopy exam conducted during pre-surgery assessments.

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2. Following the creation of the initial incision in the clear cornea, ~100 μ L of aqueous humor will be sampled from the anterior chamber via provided tuberculin syringe with 30 ga needle. The sample will be treated as described in [Appendix 1](#).
3. After the removal of the aqueous humor sample, implants will be recovered from the anterior chamber.
4. A stream of buffered saline solution (BSS) is directed to the iridocorneal angle location where the implant(s) have been identified until implant(s) is/are dislodged from the iridocorneal angle and float in the anterior chamber. Utrata forceps or an equivalent instrument is used to grasp the implant(s) one at a time and remove the implant(s) through the incision in the clear cornea created for cataract removal and IOL implantation.
5. The aqueous humor samples and recovered implants will be treated as described in [Appendix 1](#).

5.9.3. Post-Surgical Assessments, Cohort 1

The post-surgical assessments will be conducted according to the discretion of the principal investigator per established protocols. Any observations associated with a standard cataract extraction followed by intraocular lens implantation as conducted by the principal investigator per established protocols, such as expected levels of aqueous cells or flare, will be recorded as AEs. Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~12:00 p.m.); however, at the discretion of the investigator, patients will be permitted to leave the clinic after completing all procedures and assessments. Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.1.2](#). IOP lowering medications can be prescribed per the judgement of the principal investigator at this time.

5.10. Visit 10/Day 33 to 38/Follow-up, Cohort 1

Patients will be queried about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented. Any observations associated with a standard cataract extraction followed by intraocular lens implantation as conducted by the principal investigator per established protocols, such as expected levels of aqueous cells or flare, will be recorded as AEs.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform pupil measurement

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3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes)
6. Perform gonioscopy
7. Perform pachymetry (contact)
8. Assess VF
9. Perform anterior chamber OCT
10. Perform dilated funduscopy exam
11. Perform physical examination (can be performed anytime during the site visit and does not need to follow the order as written)
12. Assess vital signs (can be performed anytime during the site visit and does not need to follow the order as written)
13. Collect non-fasting blood and urine for clinical laboratory tests and systemic PK
14. If female of childbearing potential, perform urine or serum pregnancy test

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~10:00 a.m.). Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 5.3.4](#).

5.11. Visit 11/Day 42 to 49/Study Exit, Cohort 1

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented. Any observations associated with a standard cataract extraction followed by intraocular lens implantation as conducted by the principal investigator per established protocols, such as expected levels of aqueous cells or flare, will be recorded as AEs.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes)

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5. Perform specular microscopy (non-contact)
 - Non-contact specular microscopy can be performed anytime during the site visit and does not need to follow the order as written.
6. Complete the exit form
7. Discharge the patient from the trial

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~10:00 a.m.). The patient will exit the trial barring any clinically significant, possibly related or related unresolved AEs.

5.12. Unscheduled Visits, Cohort 1

Patients may need to be seen at other times than the scheduled study visits for additional safety assessments or to follow-up, as medically necessary, on changes in clinical status or to follow-up on clinical laboratory or other findings. If an additional study visit occurs, the date and nature of the visit will be documented.

During unscheduled visits, query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Only study eye will be evaluated at the listed ophthalmic assessments, with additional evaluations carried out as deemed necessary per the investigator's discretion:

1. Assess BCVA (ETDRS) with manifest refraction
 - If dilation is required to properly conduct BCVA (ETDRS) with manifest refraction the assessment should be performed after the slit lamp biomicroscopy and IOP measurement.
2. Measure IOP at 8:00 a.m. (\pm 30 minutes) or when feasible

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6. TREATMENT OF PATIENTS, COHORT 1

6.1. Treatments to be Administered, Cohort 1

6.1.1. Implantation of ENV515, Cohort 1

Treatment consisted of a single intracameral injection of ENV515 (travoprost) Intracameral Implant(s) into a pre-surgical eye that was scheduled for cataract removal. A single drop of TRAVATAN Z was administered into the non-study eye as indicated daily from Visit 3 (Day 1) to Day 24, one day prior to Visit 8 (Day 25 \pm 1 day). TRAVATAN Z was collected from the patients during Visit 8 (Day 25, \pm 1 day).

At the randomization/treatment visit (Visit 3), patient's pre-surgical eye was assigned to 1 of the dose levels of ENV515 and patients received 1 to 3 ENV515 (travoprost) Intracameral Implant(s) into the pre-surgical eye via intracameral injection administered via the provided intracameral implant applicator. All investigators were trained in implant loading, administration and retrieval by Envisia. The site received randomization information based on randomization schedule following Visit 2 specifying which ENV515 formulation (ENV515-1 or ENV515-3) and how many implants to administer. The randomization code for this open-label study was computer-generated. To randomize a patient (Visit 3), the investigator (or designee) confirmed in the eCRF that the patient remains qualified for the study. The eCRF automatically assigned the dose and number of implants that the patient was to receive based on a prospectively prepared computer generated code list.

The study treatment assignment of 1 of 4 dose levels of ENV515 to be administered was determined by the randomization code. ENV515-1 and ENV515-3 (travoprost) Intracameral Implant(s) were supplied in sterile glass vials with 1 implant per vial. The sterile implant applicator was provided in a Tyvek[®] pouch. The packages were opened and the implant applicator and the implants were placed into a sterile field. The implants were loaded into the implant applicator by the investigator immediately prior to dosing. The implant size (ENV515-1 or ENV515-3) and the number of implants to load into the implant applicator was determined based on the randomization code identifying 1 of 4 dose levels described in [Section 3.2.1](#). Additionally, the study eye was administered topical antibiotic VIGAMOX following the completion of the pre-dose assessments ([Section 5.3.1](#)) and immediately before and after the ENV515 implant administration as described below. The following instructions were distributed with the ENV515 implants and implant applicator:

Opening Instructions, Cohort 1

1. Use sterile technique in sterile field to open primary packaging for the applicator and ENV515 implants.
2. Open ENV515 Phase 2a Implant Applicator packaging and place the sterile ENV515 applicator into sterile field.
3. Do not open glass vial containing implants until ready to load into the applicator.

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Instructions for Loading the Implant into the Applicator by the Principal Investigator, Cohort 1

1. Load ENV515 implant(s) into the ENV515 Phase 2a implant applicator in a sterile field using sterile technique via insertion through the beveled needle end. The implant type (ENV515-1 or ENV515-3) and the number of implants will be specified in the randomization code.

Instructions for Administration by Principal Investigator, Cohort 1

1. Treat subject's ocular surface with topical anesthetic (proparacaine 0.5% or equivalent).
2. Treat subject's ocular surface, periocular skin, eyelid margins and eyelashes with povidone iodine and wait 2 minutes.
3. Insert lid speculum.
4. Instill one drop of VIGAMOX into the study eye.
5. Administer the implant(s) into the anterior chamber via intracameral injection through clear, peripheral cornea. The needle should be advanced parallel with the iris, ~1 mm anterior to the limbus with the subject sitting at the slit lamp, or with the subject supine under the operating scope.
6. Instill one drop of VIGAMOX into the study eye.

One implant applicator and 5 glass vials with one ENV515-1 or ENV515-3 implant/vial will be packaged in an appropriately labeled carton. The label on the package will minimally contain the following information: each package contains no less than 5 glass vials with either one ENV515-1 or ENV515-3 implant/vial and one ENV515 implant applicator; study ENV515-01, storage temperature, and "Caution: Limited by Federal (or United States) Law to Investigational use". An unmasked disclosure panel will be displayed on the bottle label of the study medication and will minimally contain the following information: ENV515-01, and name of product. The study medications will be stored in a secure area with limited access to study personnel under refrigerated storage at approximately 2 to 8°C.

6.1.2. TRAVATAN Z for Non-Study Eye, Cohort 1

TRAVATAN Z will be provided for the non-study eye with its original packaging, labeling, and instructions for use (non-study eye only).

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7. ASSESSMENT OF EFFICACY, COHORT 1

Assessments of efficacy included:

- IOP measurements completed at all visits. A diurnal curve of IOP measurements will be completed on Visit 2/Baseline and Visit 8/Treatment Day 25.

The IOP assessments and their timing are outlined in [Table 1](#) and [Section 5](#).

8. ASSESSMENT OF SAFETY, COHORT 1

8.1. Safety Parameters, Cohort 1

Safety and tolerability of ENV515 were evaluated using the following assessments:

- Specular microscopy (non-contact)
- Slit-lamp biomicroscopy
- Corneal staining
- Dilated fundus examination
- Gonioscopy exam
- Anterior chamber OCT exam
- Pupil measurement
- Pachymetry (contact)
- BCVA
- VF
- Physical examination
- Vital signs
- Non fasting clinical laboratory tests (chemistry and hematology)
- Serum or urine pregnancy tests for females of childbearing potential
- AEs

These assessments and their timing are outlined in [Table 1](#) (Cohort 1 Time and Events Schedule) and [Section 5](#). Compliance with study drug administration was also be assessed ([Section 16.3](#)).

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9. TRIAL OBJECTIVES AND PURPOSE, COHORTS 2 AND 3

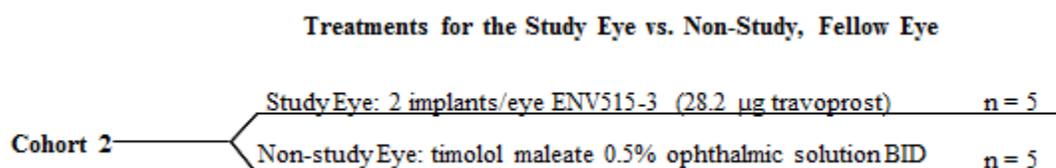
The primary objective of the Cohort 2 and 3 phases of this study is to:

- Evaluate in a dose escalating design the long-term safety and tolerability of a single, unilateral low dose of two ENV515-3 (travoprost) intracameral implants/eye in Cohort 2; and low and high doses of one and two ENV515-3-2 (travoprost) intracameral implants/eye, respectively, in Cohort 3 in patients with bilateral ocular hypertension or primary open-angle glaucoma; and

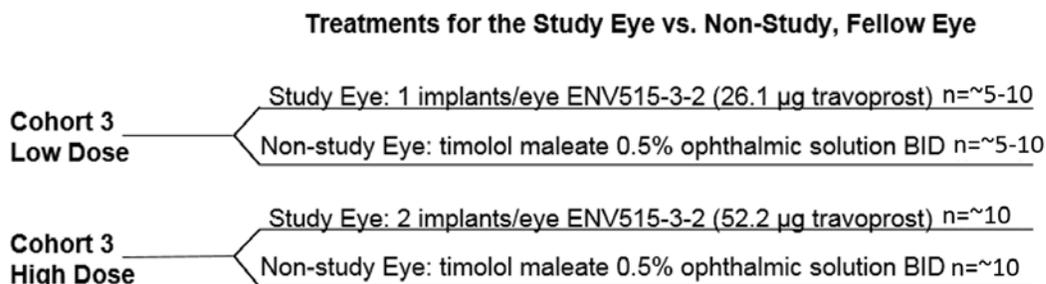
10. TRIAL DESIGN, COHORTS 2 AND 3

Cohorts 2 (5 patients) and 3 (15 patients) are 12-month, prospective, open-label, active-comparator-controlled, multicenter, dose escalating cohorts of this Phase 2a trial. Cohort 2 had a 6-month optional Extension 1 followed by an additional 3-month optional Extension 2 (for up to a total of 21 months), increasing the total study duration to approximately 23 months. Cohort 3 has a 6-month optional Extension 1 followed by an additional 6-month optional Extension 2 (for a total of 24 months), increasing the total study duration to approximately 26 months. Cohorts 2 and 3 were designed to assess the long-term safety, tolerability, and systemic exposure to travoprost after a single low dose (ENV515-3) in Cohort 2; and single low or high doses of (ENV515-3-2) in Cohort 3 in patients with bilateral open-angle glaucoma or ocular hypertension (see inclusion criteria in [Section 11.1](#)). For the purposes of the Cohorts 2 and 3, patients are eligible if in the opinion of the investigator they have an IOP in both eyes that is considered to be adequately controlled at the screening visit, can be safely withdrawn from IOP medications in both eyes during the washout period, and are not considered to be at significant risk for disease progression throughout the trial. The dose levels of travoprost in Cohorts 2 and 3 of this study are achieved by administration of a single, unilateral intracameral injection of each formulation with 28.2 µg travoprost/eye in Cohort 2; and 26.1 µg and 52.2 µg travoprost/eye in Cohort 3. These dose levels will be achieved via two implants per eye for low dose of ENV515-3 in Cohort 2; and one and two implants per eye for the low and high doses of ENV515-3-2, respectively, in Cohort 3. The study eye is prospectively defined as the eye with higher IOP or the left eye if IOP values are equal in both eyes on Dosing Visit (Day 1). All non-study eyes will receive open-label timolol maleate 0.5% ophthalmic solution administered twice a day ([Figure 4](#) and [Figure 5](#)).

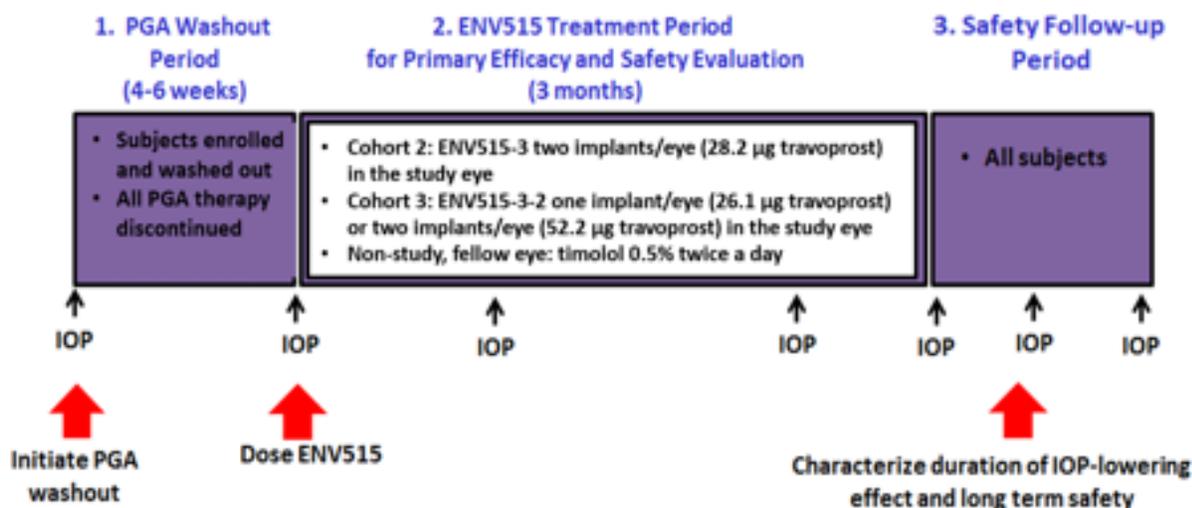
Figure 4: ENV515 Treatment, Cohort 2



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Figure 5: ENV515 Treatment, Cohort 3


On the Day 1 Dosing (Visit 3), low dose of ENV515-3 in Cohort 2, or low or high doses of ENV515-3-2 in Cohort 3 will be administered. Following Day 84 of the treatment phase (Dosing Visit 3/Day 1 to Treatment Visit 7/Day 84 [± 7 days]), an analysis of IOP treatment effect as a change in mean diurnal IOP from mean diurnal IOP baseline will be conducted as the primary efficacy outcome measure. Following the completion of the rest of the study treatment period Month 4 (Visit 8) to Exit/Early Exit (Visit 16, Visit 22, or Visit 25) for the Cohort 2 alone, all safety and tolerability analyses will be conducted (Figure 6).

Figure 6: Study Design for ENV515-01 (Cohorts 2 and 3)


For Cohort 2, the study design included up to 26 clinic visits over approximately 23 months (12 months of Cohort 2, 6-month optional Extension 1, and 3-month optional Extension 2). For Cohort 3, the study design includes up to 28 clinic visits over approximately 26 months (12 months of Cohort 3, 6-month optional Extension 1, and 6-month optional Extension 2). Following the Screening Visit, patients will be required to washout current glaucoma medication(s) (Section 16.1) for 4 weeks with up to an additional 2-week extension or 6 weeks

depending on Cohort. Patients will be required to return for an IOP baseline check during the Baseline Visit (Visit 2/Day -7 to -1) following the wash-out period. A single dose of ENV515-3 (two implants/eye) or ENV515-3-2 (one or two implant(s)/eye) will be given via intracameral injection during Dosing Visit 3/Day 1.

Patients will receive the following investigational product doses in the study eye on Day 1 Dosing (Visit 3) and will receive timolol maleate 0.5% ophthalmic solution to use in the non-study eye twice daily starting on the evening of Day 1 and continuing through the day prior to Month 12 (Visit 16), Month 18 (Visit 22), or Month 21 (Visit 25) for Cohort 2 or Month 24 (Visit 28) for Cohort 3.

- Cohort 2 low dose level: two implants/eye of ENV515-3 (28.2 µg/eye)
- Cohort 3 low and high dose levels:
 - one implant/eye of ENV515-3-2 (26.1 µg/eye)
 - two implants/eye of ENV515-3-2 (52.2 µg/eye)

Diurnal IOP curves will be measured at select study visits with the exception of the abbreviated visits at the Screening Visit (Days -49 to -42 for Cohort 2 and Days -56 to -42 for Cohort 3) Dosing Visit 3 (Day 1), Treatment Visit 4 (Day 2), and Treatment Visit 5a (Day 28), and selected visits depending on the Cohort and Extension(s).

Throughout the study, patients will undergo multiple safety assessments. A schedule of assessments is outlined in the sections below and in [Table 1](#), [Table 2](#), [Table 3](#), [Table 4](#), [Table 5](#), [Table 6](#), and [Table 7](#).

10.1. Safety Evaluations, Cohorts 2 and 3

10.1.1. Review of Safety Data by Medical Monitor, Cohorts 2 and 3

A review of unmasked ocular safety data from each patient will be performed on an ongoing basis by a medical monitor. All ocular safety data for each patient will be provided to the medical monitor as it is generated throughout the trial. A patient may be discontinued at any time during the study at the discretion of the medical monitor for reasons referenced in, but not limited to [Section 15.2.1](#). In addition, a meeting with the Envisia project team may be requested by the medical monitor at any time during the study to conduct a full evaluation of safety, which may result in a recommendation to terminate the study.

10.2. Safety Endpoints, Cohorts 2 and 3

The safety endpoints of the Cohorts 2 and 3 phases of this study are:

- Incidence of AEs;
- Changes in ophthalmic examination parameters (slit-lamp biomicroscopy, corneal staining, dilated funduscopy exam, anterior segment photos, pupil measurement,

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ocular symptom questionnaire, and VF as measured by the Humphrey Field Analyzer using program 24-2);

- Changes in endothelial cell count and endothelial cell morphology using specular microscopy;
- Changes in corneal thickness as measured using pachymetry;
- Changes in IOP, including diurnal curve, as measured using a Goldmann applanation tonometer;
- Changes in BCVA with manifest refraction using the ETDRS chart;
- Changes in body systems assessment, vital signs, and laboratory parameters;
- Rate of discontinuation from the study; and
- Drug levels (travoprost free acid) in plasma.

10.3. Endpoints, Cohorts 2 and 3

10.3.1. Trial Treatments, Cohorts 2 and 3

The single low dose of 28.2 µg travoprost/eye will be achieved via two ENV515-3 implants/eye in Cohort 2. Single low and high doses of 26.1 and 52.2 µg/eye travoprost will be achieved via one or two ENV515-3-2 implants/eye, respectively, in Cohort 3 dosed into the study eye, with the non-study eye receiving timolol maleate 0.5% ophthalmic solution dosed twice a day.

10.3.2. Study Eye Selection

The central reading centers will determine eligibility of one or both eyes based on inclusion criteria related to corneal endothelial cell counts and anterior chamber angles assessed at Screening (Visit 1). At least one of the eyes must meet both inclusion criteria of cell counts and angle in addition to the other eligibility criteria. If both eyes are eligible, the study eye is defined as the eye with the higher mean diurnal IOP at Baseline (Visit 2) or the left eye if the mean diurnal IOP values are equal for both eyes at Baseline (Visit 2).

10.4. Methods to Minimize Bias in Cohorts 2 and 3

Patients were prospectively assigned to one dose of ENV515-3 in Cohort 2. In Cohort 3 ENV515-3-2 will be administered into the study eye, starting with the high dose level first (n=9) and proceeding to the low dose (n=6). The study eye is prospectively assigned based on predefined criteria ([Section 11.3](#) and [Section 11.4](#)). The non-study eye will receive timolol maleate 0.5% ophthalmic solution. The patients, investigators, site staff, and project teams at Envisia, and the medical monitor, will be unmasked to treatment assignment.

11. SELECTION AND WITHDRAWAL OF PATIENTS, COHORTS 2 AND 3

11.1. Patient Inclusion Criteria, Cohort 2

Individuals of either gender or any race will be eligible for study participation in Cohort 2 if they:

1. Are male or female between 18 and 85 years of age.
2. Have a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma.
3. Normal appearing anterior chamber angles (Shaffer classification Grade 3 or 4, with an angle of at least 20° determined by gonioscopy, and confirmed to have an open angle as determined by anterior chamber OCT evaluated by a central reading center prior to dosing).
4. Are currently treated with topical PGA for ocular hypertension in both eyes.
5. Patients who in the opinion of the investigator: have an IOP in both eyes that is considered to be adequately controlled at the Screening Visit (Visit 1); can be safely withdrawn from IOP medications in both eyes during the washout period, and who are not considered to be at significant risk for disease progression throughout the trial.
6. At the Baseline Visit after washout (Visit 2), have IOP measurements that meet all of the following:
 - a. Have an IOP at 8:00 a.m. (± 30 minutes) and at 10:00 a.m. (± 30 minutes) between 22 and 34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes
 - b. Have an IOP at 4:00 p.m. (± 30 minutes) between 19 and 30 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye
7. At the Dosing Visit (Visit 3), have IOP measurement that is between 22 and 34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes.
8. Have endothelial cell counts of at least 2000 cells/mm² and normal endothelial cell morphology prior to dosing as evaluated by central reading center.
9. If female, patients must be incapable of pregnancy because of hysterectomy, tubal ligation or have been amenorrheic for at least 2 years. Female patients must have a negative pregnancy test and not be nursing. If female patient is capable of pregnancy, she must use effective (e.g. double barrier) method of birth control for the duration of the study.
10. Must be able to provide a written informed consent to participate in the study, in accordance with the international Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and local regulations, before initiating any study-related procedures.

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11.2. Patient Exclusion Criteria, Cohort 2

Individuals of either gender or any race will not be eligible for study participation in Cohorts 2 if they:

1. Are diagnosed with closed angle glaucoma, exfoliation syndrome or exfoliation glaucoma, pigment dispersion or secondary glaucoma.
2. Are insufficiently responsive to PGA topical treatment, i.e., are PGA non-responders.
3. Have a history of glaucoma-related surgery (e.g., trabeculectomy, cryotherapy, laser iridotomy and minimally invasive procedures including shunts/stents).
4. Have severe glaucoma with a mean defect (MD) worse than -8.0, a central island of vision, or otherwise severe glaucoma that would not tolerate a short-term increase in IOP.
5. According to the investigator's best judgment, are at risk for progression of glaucoma, VF or VA worsening as a consequence of participation in the trial.
6. Have any abnormality preventing reliable applanation tonometry in either eye.
7. Have a central corneal thickness less than 500 micrometers or greater than 600 micrometers as determined by pachymetry at the Screening Visit (Visit 1).
8. Have a history of recurrent corneal erosion syndrome, multiple corneal abrasions, or an abrasion that was slow to heal.
9. Have had intraocular conventional surgery, intraocular laser surgery, corneal refractive surgery or eyelids surgery within the past 3 months. Complicated cataract surgery that resulted in intraocular lens placement outside the capsular bag or a break in the posterior capsule is not allowed.
10. Are currently diagnosed with active infectious/noninfectious conjunctivitis, or moderate to severe blepharitis in either eye. (Chronic mild blepharitis or injection related to mild blepharitis, lid lag, mild dry eye or seasonal allergies are allowed.)
11. Are currently taking or have taken corticosteroids (oral, ocular, injectable, IV) or used dermatology formulations of steroids in the vicinity of eyes in the 1 month prior to Visit 1; have a history of chronic ocular corticosteroid (topical or intraocular) use within the past year. Inhaled, intranasal, or topical (dermal) steroids not in the vicinity of the eyes is permissible if on a stable dose for at least 1 month prior to Visit 1.
12. Have any media opacity or are uncooperative in such a way that restricts adequate examination of the ocular fundus or anterior chamber in either eye.
13. Are unwilling to discontinue use of contact lenses for the duration of their study participation.
14. Have progressive retinal or optic nerve disease apart from glaucoma or history of uveitis or keratitis.

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15. Have any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial such as travoprost or poly-lactic acid or similar excipients, topical anesthetic (proparacaine 0.5% or equivalent), iodine, timolol maleate and VIGAMOX[®] (or generic equivalent).
16. Have a requirement for any ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Visit 2.
17. Have a history, or a suspected history of drug or alcohol dependence in the preceding year.
18. Currently using or used marijuana in the past 30 days prior to Visit 1.
19. Have received any investigational product within the past 30 days prior to Visit 1.
20. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same
21. Patients who, per investigator's judgment, are not good clinical trial candidates due to personal (e.g., perceived willingness or ability to comply with protocol, significant traveling distance to medical center) and/or medical (i.e. mental illness, other non-ocular medical conditions, or laboratory abnormalities that might negatively impact trial participation or outcome) conditions that would likely impede the patient's successful study completion or planned analyses.

11.3. Patient Inclusion Criteria, Cohort 3

Individuals of either gender or any race will be eligible for study participation in Cohort 3 if they:

1. Are male or female between 18 and 85 years of age.
2. Have a diagnosis of bilateral ocular hypertension or primary open-angle.
3. Normal appearing anterior chamber angles (Shaffer classification Grade 3 or 4, with an angle of at least 20° determined by gonioscopy, and confirmed to have an open angle as determined by anterior chamber OCT evaluated by a central reading center prior to dosing in the study eye).
4. Are currently treated with topical PGA for ocular hypertension in both eyes. (Dual therapy (i.e. PGA and another IOP lowering agent) is acceptable)
5. In the opinion of the investigator, the non-study eye can be adequately controlled with timolol maleate 0.5% ophthalmic solution BID.
6. Patients who in the opinion of the investigator, have an IOP in both eyes that is considered to be adequately controlled at Screening (Visit 1), can be safely withdrawn from IOP medications in both eyes during the washout period, and who are not considered to be at significant risk for disease progression throughout the trial.

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7. At Baseline (Visit 2) after washout, have IOP measurements that meet all of the following:
 - a. Have an IOP at 8:00 a.m. (± 30 minutes) and at 10:00 a.m. (± 30 minutes) between 22 and 34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes
 - b. Have an IOP at 4:00 p.m. (± 30 minutes) between 19 and 30 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye
 - c. Demonstrate an 8 AM IOP increase of at least 4 mmHg in each eye Baseline (Visit 2) compared to the Screening (Visit 1) IOP measurements.
8. At Dosing (Visit 3), have IOP measurement that is between 22 and 34 mm Hg in both eyes with a ≤ 4 mm Hg difference between the eyes.
9. Have endothelial cell counts of at least 2000 cells/mm² and normal endothelial cell morphology at Screening (Visit 1) as evaluated by central reading center in the study eye.
10. If female, patients must either be incapable of pregnancy because of hysterectomy, tubal ligation or have been amenorrheic for at least 2 years or must use effective (e.g., double barrier) method of birth control for the duration of the study. Female patients must have a negative pregnancy test, and not be nursing
11. Must be able to provide a written informed consent to participate in the study, in accordance with the international Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and local regulations, before initiating any study-related procedures.

11.4. Patient Exclusion Criteria, Cohort 3

Individuals of either gender or any race will not be eligible for study participation in Cohort 3 if they:

1. Are diagnosed with closed angle glaucoma, exfoliation syndrome or exfoliation glaucoma, pigment dispersion or secondary glaucoma in either eye.
2. Are insufficiently responsive to PGA topical treatment, i.e., are PGA non-responders in either eye.
3. Have a history of glaucoma-related surgery (e.g., Selective Laser Trabeculoplasty (SLT), Argon Laser Trabeculoplasty (ALT), trabeculectomy, cryotherapy, laser iridotomy and minimally invasive procedures including shunts/stents) in the study eye.
4. Have severe glaucoma with a mean defect (MD) worse than -8.0, a central island of vision, or otherwise severe glaucoma that would not tolerate a short-term increase in IOP including advanced cupping in either eye.
5. Have manifest refraction BCVA worse than 20/80 Snellen in either eye as measured using an ETDRS chart in.
6. Have hyperemia score of 1 or greater at Baseline (Visit 2).

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7. According to the investigator's best judgment, are at risk for progression of glaucoma, VF or VA worsening as a consequence of participation in the trial in either eye.
8. Have any abnormality preventing reliable applanation tonometry in either eye.
9. Have a central corneal thickness less than 500 micrometers or greater than 600 micrometers as determined by pachymetry at Screening (Visit 1) in either eye.
10. Have a history of recurrent corneal erosion syndrome, multiple corneal abrasions, or an abrasion that was slow to heal in either eye.
11. Have had intraocular conventional surgery, intraocular laser surgery, corneal refractive surgery or eyelids surgery within the past 3 months in the study eye. Complicated cataract surgery that resulted in intraocular lens placement outside the capsular bag or a break in the posterior capsule in the study eye is not allowed.
12. Are currently diagnosed with active infectious/noninfectious conjunctivitis, or moderate to severe blepharitis in either eye. (Chronic mild blepharitis or injection related to mild blepharitis, lid lag, mild dry eye or seasonal allergies are allowed.)
13. Are currently taking or have taken corticosteroids (oral, ocular, injectable, IV) or used dermatology formulations of steroids in the vicinity of eyes in the 1 month prior to Screening (Visit 1); have a history of chronic ocular corticosteroid (topical or intraocular) use within the past year. Inhaled, intranasal, or topical (dermal) steroids not in the vicinity of either eye is permissible if on a stable dose for at least 1 month prior to Screening (Visit 1).
14. Have any media opacity or are uncooperative in such a way that restricts adequate examination of the ocular fundus or anterior chamber in either eye.
15. Are unwilling to discontinue use of contact lenses for the duration of their study participation.
16. Have progressive retinal or optic nerve disease apart from glaucoma or history of uveitis or keratitis in either eye.
17. Have any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial such as travoprost or poly-lactic acid or similar excipients, topical anesthetic (proparacaine 0.5% or equivalent), iodine, timolol maleate, and VIGAMOX[®] (or generic equivalent).
18. Have a requirement for any ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Baseline (Visit 2).
19. Have a history, or a suspected history of illicit drug or alcohol dependence in the preceding year.
20. Currently using or used marijuana in the past 30 days prior to Screening (Visit 1).

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21. Have received any investigational product within the past 30 days prior to Screening (Visit 1) or have ever been previously implanted in the anterior segment with experimental therapies.
22. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same
23. Patients who, per investigator's judgment, are not good clinical trial candidates due to personal (e.g., perceived willingness or ability to comply with protocol, significant traveling distance to medical center) and/or medical (e.g., mental illness, other non-ocular medical conditions, or laboratory abnormalities that might negatively impact trial participation or outcome) conditions that would likely impede the patient's successful study completion or planned analyses.

11.5. Dosing Criteria, Cohorts 2 and 3

At the Dosing Visit (Visit 3/Day 1), an eligible patient must:

- Continue to meet all inclusion/exclusion criteria as defined in [Section 11.1](#), [Section 11.2](#), [Section 11.3](#), and [Section 11.4](#) depending on cohort.

11.6. Patient Rescue Criteria, Cohorts 2 and 3

For Cohort 2 and its Extensions 1 and 2, rescue therapy may be allowed in the study eye if in the opinion of the investigator the IOP is not well controlled on any two visits after Day 1 that are separated by at least 4 weeks. If IOP is well controlled, rescue therapy should be discontinued and the patient should resume regular study visit schedule. Each patient can be subjected to up to two rescue treatments. If rescue therapy is needed after 2 prior rescue therapy periods or after 7 months post-dose, the patient should be permanently rescued until the completion of the study.

For Cohort 2 and its Extensions 1 and 2, AZOPT[®] (brinzolamide ophthalmic suspension) 1% will be used for rescue therapy. Patients will be given four weeks of AZOPT treatment 3 times daily and evaluated at their next study visit. If IOP is well controlled, rescue therapy should be discontinued and patients should resume the regular study visit schedule per protocol. At the investigator's discretion, the patient can be brought in for an unscheduled visit two weeks following the discontinuation of AZOPT for an IOP assessment. The investigator can choose to measure IOP at 8 AM or full diurnal. If the IOP is well controlled during the unscheduled visit, the patient should resume the regular study visit schedule. If the patient's IOP is not well controlled during the unscheduled visit, the patient should be permanently rescued with Timolol maleate 0.5% ophthalmic solution twice a day until the completion of the study. Thus, each patient can be subjected to only one AZOPT rescue treatment. Notwithstanding the above, both the study and non-study eyes may be rescued at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

For Cohort 3 and its Extension 1, rescue therapy may be allowed in the study eye if, in the opinion of the investigator, the IOP is not well controlled on any two visits after Month 3 (Day 84) that are separated by at least 4 weeks (+/- 7 days). Timolol maleate 0.5% ophthalmic

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solution administered BID daily will be used for rescue therapy. The patient should be permanently rescued with Timolol maleate 0.5% ophthalmic solution twice a day until the completion of the study. Notwithstanding the above, both the study and non-study eyes may be rescued at any time, at the investigator's discretion, if it is considered to be in the best interest of the patient.

11.7. Patient Withdrawal Criteria, Cohorts 2 and 3

Any patient who wishes to withdraw from the study on his or her own accord for any reason is entitled to do so without obligation. Patients who are withdrawn from the study prior to dosing will be replaced. Any patient may be removed from the study by the investigator if it is deemed necessary for the patient's safety.

In the event that withdrawal of a dosed patient is medically necessary or requested by the patient, the investigator should make every attempt to complete all assessments indicated at the Early Exit/Exit (Visit 16 for Cohorts 2 and 3, Visit 22 for Cohort 2 Extension 1, Visit 25 for Cohort 2 Extension 2; and Visit 22 for Cohort 3 Extension 1).

If patient withdrawal is required due to a treatment related AE or SAE and the implant removal is necessary prior to its biodissolution, the removal of the ENV515-3 or ENV515-3-2 implant(s) should occur as soon as possible based on the judgment of the investigator and safety of the patient.

If an treatment related AE or SAE is unresolved at the time of the patient's final study visit, an effort will be made to follow the patient until the AE or SAE is resolved or stabilized (Section 17), the patient is lost to follow-up, or there is some other resolution of the event. The investigator should make every attempt to follow all SAEs to resolution.

Following ongoing review of the data by the medical monitor, any individual patient safety concerns will be discussed between Envisia representative and investigator. If the investigator determines that a patient should be discontinued and withdrawn from the study, the removal of the ENV515 implants should occur as soon as possible based on the judgment of the investigator.

A patient may be discontinued and withdrawn from the study at any time at the discretion of the investigator for any safety reason, including but not limited to those listed below:

- IOP measurement of 35 mm Hg or greater in either eye at any measurement
- Any clinically significant pole changes, including but not limited to:
 - Progressive VF loss or optic nerve changes
 - CME
 - Other significant disease such as AMD or vascular occlusion
- Pachymetry measurement of the central corneal thickness which reveals a change that falls outside of the normal variability when compared to the baseline measurement

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- An acute increase of 15% or greater in corneal thickness for a period of <24 hours after the instillation of study drug
- A chronic increase of 10% or greater in corneal thickness for a period of >24 hours after the instillation of study drug
- A $\geq 30\%$ decrease in central endothelial cell density as evaluated by the centralized reading center

In the event that study discontinuation and withdrawal of a subject is necessary, the investigator should make every attempt to complete all protocol safety assessments and visits. Unless consent has been withdrawn, any subject is considered to be in the treatment phase of the study until the completion of the study, and such subjects should continue to be followed and will be expected to complete all safety assessments and visits.

11.8. Early Exit Criteria, Cohorts 2 and 3

Patients may also exit the study sooner than their exit visit if all of the following are true:

- They have received rescue therapy
- Their IOP in the study eye is well controlled
- No implant remnants are visible by gonioscopy on two consecutive visits
- No treatment related adverse events are present that require continued monitoring.

12. PROCEDURE SCHEDULE BY STUDY VISIT, COHORT 2

12.1. Visit 1/-49 to -29 days/Screening Evaluation, Cohort 2

At Visit 1, patients will be screened, and if eligible, enrolled into the study. Before any study specific assessments are performed, written informed consent will be obtained from each patient. Screening procedures can be conducted over several visits but should be completed within a 7 day period. During the visit, the procedures described below will be performed.

12.1.1. Screening Assessments

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Obtain written informed consent
2. Obtain medical history, ocular history, and demographics (can be performed anytime during the visit)
3. Evaluate and record patient's medication usage (including concomitant medications taken within the past 30 days) (can be performed anytime during the visit)
4. Assess BCVA (ETDRS) with manifest refraction
5. Perform pupil measurement
6. Perform slit lamp biomicroscopy
7. Perform corneal staining
8. Measure IOP at 8 a.m.
9. Perform gonioscopy
10. Perform pachymetry (contact)
11. Perform specular microscopy, non-contact (can be performed anytime during the visit beyond the pachymetry exam)
12. Assess VF
13. Perform anterior chamber OCT
14. Perform dilated funduscopy exam
15. Perform body system assessment (can be performed anytime during the site visit)
16. Assess vital signs (can be performed anytime during the site visit)
17. Collect non-fasting blood and urine for clinical laboratory tests (can be performed any time after the 10 a.m. IOP measurements)
18. If female of childbearing potential, perform urine pregnancy test
19. Verify that patient meets all applicable entry criteria

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20. Begin washout of patient's current PGA therapy.
21. Query patient about whether or not they have experienced symptoms during the exam procedures suggesting an AE. AEs will be documented.

The patient will be asked to return for the baseline visit after 4 weeks. The washout period may be extended up to two additional weeks if it remains safe for the patient, and to accommodate the patient's or the investigator's schedule.

Before subjects leave the clinic, they should receive an appointment for their next study visit and the following instructions:

- Discontinue use of all eye drop medications until the end of the study (if appropriate). With your doctor's approval, you may be able to use artificial tear eye drops.
- At all visits except Visit 3 and Visit 4, be prepared for a long clinic visit. You will be expected to have IOP measurements at 8:00 a.m., 10:00 a.m., and 4:00 p.m. You may leave the clinic after the 10:00 a.m. assessments with your doctor's approval.
- Call your study site if you have any problems.
- Remember not to wear contact lenses

12.2. Visit 2/Day -7 to -1/Baseline, Cohort 2

Patients will be queried about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

12.2.1. Baseline Assessments

Assessments will be conducted in the following general order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m.
 - IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 8:00 a.m. (± 30 minutes)
 - IOP must increase of at least 4 mmHg in each eye compared to the pre-washout baseline
6. Perform gonioscopy
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) (can be performed anytime during the visit)

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9. Assess vital signs (can be performed anytime during the site visit)
10. Measure IOP at 10:00 a.m. (± 30 minutes)
 - IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 10:00 a.m. (± 30 minutes)
11. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed after the 10 a.m. IOP)
12. If female of childbearing potential, perform urine pregnancy test
13. Measure IOP at 4:00 p.m. (± 30 minutes)
 - IOP must be between 19-30 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 4:00 p.m. (± 30 minutes)
14. Perform dilated fundoscopic examination
15. Verify that patient meets all entry criteria

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

12.3. Visit 3/Day 1/Dosing/Treatment, Cohort 2

Query patient about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

12.3.1. Pre-dose Assessments

Assessments will be conducted in the following general order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at between 6:00 a.m. and 10:00 a.m. (± 30 minutes)
5. Perform gonioscopy
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only
8. Instill one drop of VIGAMOX into the study eye
9. Verify that patient meets all entry criteria

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12.3.2. Study Eye Assignment and Study Drug Administration

Patients will be assessed to ensure they still qualify to participate in the study based on the inclusion/exclusion criteria ([Section 11.3](#) and [Section 11.4](#)). The patient's study eye will be assigned to receive 2 ENV515-3 (travoprost) Intracameral Implant(s) into the study eye via intracameral injection administered via the provided intracameral implant applicator. The study-trained investigator will administer the dose of study medication into the study eye between 6:00 a.m. and 10:00 a.m. (± 30 minutes). Timolol maleate 0.5% ophthalmic solution will be administered into the non-study eye by the patient at 8 p.m. (± 60 minutes) on the day of Visit 3.

12.3.3. Post-dose Assessments

1. Perform slit lamp biomicroscopy
2. Dispense bottle of timolol maleate 0.5% ophthalmic solution to the patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~12:00 p.m.); however, at the discretion of the investigator, patients will be permitted to leave the clinic following the completion of the dosing.

12.3.4. Patient Instructions

Before patients leave the clinic, they should receive an appointment for their next study visit and the following instructions:

- Remember to use timolol maleate 0.5% ophthalmic solution twice daily (as close to 8:00 a.m. and 8:00 p.m. as you can ± 60 minutes) in the non-study eye. **DO NOT PUT** timolol maleate 0.5% ophthalmic solution in the eye that received the ENV515 implants. Continue using timolol maleate 0.5% ophthalmic solution until one day prior to the last study visit, Visit 16 (Month 12 ± 7 days). Please remember to bring timolol maleate 0.5% ophthalmic solution with you to at each subsequent visit so that it can be administered after the 8:00 a.m. IOP measurement. It will need to be collected from you before issuing a new bottle at applicable visits.
- Continue to withhold (not use) all your other eye drop medications until the end of the study (if appropriate). With your investigator's approval, you may be able to use artificial tear eye drops.
- Remember not to wear contact lenses
- Call your study site if you have any problems
- Please avoid physical activities associated with jarring physical motions, such as horseback riding, for the rest of the study.

12.4. Visit 4/Day 2 + up to 3 Days/Treatment Period, Cohort 2

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

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Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
5. Perform gonioscopy
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~10:00 a.m.). Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.5. Visit 5/Day 14 \pm 3 Days/Treatment Period, Cohort 2

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
5. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4:00 p.m. IOP measurement)
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact)
8. Measure IOP at 10:00 a.m. (± 30 minutes)
9. Measure IOP at 4:00 p.m. (± 30 minutes)
10. If female of childbearing potential, perform urine pregnancy test
11. Collect non-fasting blood and urine for clinical laboratory tests and systemic PK (can be performed after the 10 a.m. IOP)

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12. Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement. Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.6. Visit 5a/Day 28 ± 3 Days/Treatment Period, Cohort 2

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
5. Perform gonioscopy
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only

Patients are expected to remain in the clinic for the completion of all procedures (~8:00 a.m. to ~10:00 a.m.).

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.7. Visit 6/Day 42 ± 3 Days/Treatment Period, Cohort 2

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes), please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement

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5. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only (can be performed anytime during the visit)
8. Measure IOP at 10:00 a.m. (± 30 minutes)
9. Measure IOP at 4:00 p.m. (± 30 minutes)
10. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed after the 10 a.m. IOP)
11. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.8. Visit 7/Day 84 \pm 7 Days/Treatment Period, Cohort 2

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) study eye only (can be performed anytime during the site visit)

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9. Perform anterior chamber OCT
10. Measure IOP at 10:00 a.m. (± 30 minutes)
11. Measure IOP at 4:00 p.m. (± 30 minutes)
12. Perform body system assessment (can be performed anytime during the site visit)
13. Assess vital signs (can be performed anytime during the site visit)
14. Perform dilated fundus exam
15. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed after the 10:00 a.m. IOP)
16. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.9. Visit 8/Month 4 – Visit 15/Month 11 \pm 7 Days/Treatment Period, Cohort 2

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement only at Visit 10/Month 6, and Visit 13/Month 9
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
7. Perform pachymetry (contact) only at Visits 8, 9, 10, 12, and 14
8. Perform specular microscopy (non-contact) study eye only at Visits 8, 9, 10, 12, and 14 (can be performed anytime during the site visit)

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9. Measure IOP at 10:00 a.m. (± 30 minutes)
10. Measure IOP at 4:00 p.m. (± 30 minutes)
11. Perform body system assessment (can be performed anytime during the site visit) only at Visit 10/Month 6
12. Assess vital signs (can be performed anytime during the site visit) only at Visit 10/Month 6 and Visit 13/Month 9
13. Perform dilated funduscopy examination only at Visit 10/Month 6
14. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK only at **Visits 10, 11, and 13** for clinical laboratory tests and at all visits for systemic PK (can be performed after the 10 a.m. IOP)
15. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.10. Visit 16/Month 12 \pm 7 Days/Treatment Period Study Exit, Cohort 2 (if patient chooses not to enroll in Extension 1)

If a patient discontinues prior to the Visit 16/Month 12, or declines to continue into the Cohort 2 Study Extension 1 and chooses to exit the study at Visit 16/Month 12, the following procedures are to be performed. If the patient chooses to continue into the Cohort 2 Study Extension 1, please follow the procedures in [Section 12.11](#).

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8 am (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)

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6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) for both eyes (can be performed anytime during the visit)
9. Assess VF
10. Perform anterior chamber OCT
11. Measure IOP at 10:00 a.m. (± 30 minutes)
12. Measure IOP at 4:00 p.m. (± 30 minutes)
13. Perform dilated funduscopy exam
14. Perform body system assessment (can be performed anytime during the site visit)
15. Assess vital signs (can be performed anytime during the site visit)
16. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed any time after the 10 a.m. IOP)
17. If female of childbearing potential, perform urine pregnancy test
18. Collect used timolol maleate 0.5% ophthalmic solution bottle
19. Complete the exit form
20. Discharge the patient from the trial

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

12.11. Visit 16/Month 12 – Visit 21/Month 17 \pm 7 Days/Treatment Period, Cohort 2 Study Extension 1 (if patient chooses to enroll in Extension 1)

Obtain written consent to participate in Cohort 2, Extension 1 before any study related activities begin.

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

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1. Obtain written informed consent before or at Visit 16/Month 12 to participate in Cohort 2 Extension 1
2. Assess BCVA (ETDRS) with manifest refraction
3. Perform pupil measurement only at Visit 16/Month 12, Visit 18/Month 14, and Visit 20/Month 16
4. Perform slit lamp biomicroscopy
5. Perform corneal staining
6. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
7. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
8. Perform pachymetry (contact) only at Visit 16/Month 12, Visit 18/Month 14, and Visit 20/Month 16
9. Perform specular microscopy (non-contact) study eye only at Visit 16/Month 12, Visit 18/Month 14, Visit 20/Month 16 and Visit 21/Month 17 (can be performed anytime during the site visit)
10. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image only at Visit 16/Month 12 and Visit 21/Month 17.
11. Perform body system assessment only at Visit 16/Month 12 (can be performed anytime during the site visit)
12. Assess vital signs only at Visit 16/Month 12 and Visit 19/Month 15 (can be performed anytime during the site visit)
13. Perform dilated funduscopy examination only at Visit 16/Month 12
14. Collect non-fasting blood and urine for clinical laboratory tests only at Visit 16/Month 12
15. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~9:00 a.m.).

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.12. Visit 22/Month 18 ± 7 Days/Treatment Period Study Exit, Cohort 2 Extension 1 (if patient chooses not to enroll in Extension 2)

If a patient discontinues prior to the Visit 22/Month 18, or declines to continue into the Cohort 2 Study Extension 2 the following procedures are to be performed. If the patient chooses to continue into the Cohort 2 Study Extension 2, please follow the procedures in [Section 12.13](#).

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8 am (±30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4:00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) for both eyes (can be performed anytime during the visit)
9. Assess VF
10. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
11. Measure IOP at 10:00 a.m. (±30 minutes)
12. Measure IOP at 4:00 p.m. (±30 minutes)
13. Perform dilated funduscopy exam
14. Perform body system assessment (can be performed anytime during the site visit)
15. Assess vital signs (can be performed anytime during the site visit)
16. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK
17. If female of childbearing potential, perform urine pregnancy test
18. Collect used timolol maleate 0.5% ophthalmic solution bottle
19. Complete the exit form
20. Discharge the patient from the trial

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Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~9:00 a.m.).

12.13. Visit 22/Month 18 – Visit 24/Month 20 ± 7 Days/Treatment Period, Cohort 2 Study Extension 2 (if patient chooses to enroll in Extension 2)

Obtain written consent to participate in Cohort 2, Extension 2 before any study related activities begin.

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Obtain written informed consent before or at Visit 22/Month 18 to participate in Cohort 2 Extension 2
2. Assess BCVA (ETDRS) with manifest refraction
3. Perform pupil measurement
4. Perform slit lamp biomicroscopy
5. Perform corneal staining
6. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
7. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
8. Perform pachymetry (contact)
9. Perform specular microscopy (non-contact) study eye only
10. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
11. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~9:00 a.m.).

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

12.14. Visit 25/Month 21 \pm 7 Days/Treatment Period Study Exit, Cohort 2 Study Extension 2

If a patient discontinues prior to Visit 25/Month 21, the following procedures are to be performed.

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Perform corneal staining
5. Measure IOP at 8 a.m. (\pm 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4:00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) for both eyes (can be performed anytime during the visit)
9. Assess VF
10. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
11. Measure IOP at 10:00 a.m. (\pm 30 minutes)
12. Measure IOP at 4:00 p.m. (\pm 30 minutes)
13. Perform dilated funduscopy exam
14. Perform body system assessment (can be performed anytime during the site visit)
15. Assess vital signs (can be performed anytime during the site visit)
16. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed any time during the site visit)
17. If female of childbearing potential, perform urine pregnancy test
18. Collect used timolol maleate 0.5% ophthalmic solution bottle
19. Complete the exit form
20. Discharge the patient from the trial

13. PROCEDURE SCHEDULE BY STUDY VISIT, COHORT 3

At visits with IOP diurnal measurements, patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.1.2](#).

13.1. Visit 1/Day -56 to -42/Screening Evaluation, Cohort 3

At Visit 1, patients will be screened, and if eligible, enrolled into the study. Before any study specific assessments are performed, written informed consent will be obtained from each patient. During the visit, the procedures described below will be performed. These procedures can occur over a seven day window.

13.1.1. Screening Assessments

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Obtain written informed consent
2. Obtain medical history, ocular history, and demographics (can be performed anytime during the visit)
3. Evaluate and record patient's medication usage - include concomitant medications taken within the past 30 days (can be performed anytime during the visit)
4. Assess BCVA (ETDRS) with manifest refraction
5. Perform pupil measurement
6. Perform slit lamp biomicroscopy
7. Perform corneal staining
8. Measure IOP before 10:00 a.m.
9. Perform gonioscopy
10. Perform pachymetry (contact)
11. Perform specular microscopy, non-contact (can be performed anytime during the visit beyond the pachymetry exam)
12. Assess VF
13. Perform anterior chamber OCT

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14. Perform dilated funduscopy exam
15. Perform body system assessment (can be performed anytime during the site visit)
16. Assess vital signs (can be performed anytime during the site visit)
17. Collect non-fasting blood and urine for clinical laboratory tests (can be performed any time after the 10 a.m. IOP measurements)
18. If female of childbearing potential, perform urine pregnancy test (can be performed anytime during the site visit)
19. Verify that patient meets all applicable entry criteria
20. Query patient about whether or not they have experienced symptoms during the exam procedures suggesting an AE. AEs will be documented.

At the end of the examination, patients that have met the eligibility requirements will be asked to discontinue their current glaucoma medication(s).

The patient will be asked to return for the baseline visit after 6 weeks.

13.1.2. Patient Instructions

Before patients leave the clinic, they should receive an appointment for their next study visit and the following instructions:

- Discontinue use of all eye drop medications until the end of the study (if appropriate). With your investigator's approval, you may be able to use artificial tear eye drops.
- At all visits except Visit 3 and Visit 4, be prepared for a long clinic visit. You will be expected to have IOP measurements at 8:00 a.m., 10:00 a.m., and 4:00 p.m. You may leave the clinic after the 10:00 a.m. assessments with your doctor's approval.
- Call your study site if you have any problems.
- Remember not to wear contact lenses.

13.2. Visit 2/-7 to -1 days/Baseline Assessments, Cohort 3

Patients will be queried about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following general order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy
4. Corneal photograph taken at the slit lamp

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5. Perform corneal staining
6. Measure IOP at 8:00 a.m.
 - a. IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 8:00 a.m. (± 30 minutes)
 - b. IOP must increase of at least 4 mmHg in each eye compared to the pre-washout baseline
7. Perform gonioscopy
8. Perform pachymetry (contact)
9. Perform specular microscopy (non-contact), Non-contact specular microscopy can be performed anytime during the site visit
10. Assess vital signs (can be performed anytime during the site visit)
11. If female of childbearing potential, perform urine pregnancy test (can be performed anytime during the site visit)
12. Measure IOP at 10:00 a.m. (± 30 minutes)
 - a. IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 10:00 a.m. (± 30 minutes)
13. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed after the 10 a.m. IOP)
14. Measure IOP at 4:00 p.m. (± 30 minutes)
 - a. IOP must be between 19-30 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 4:00 p.m. (± 30 minutes)
15. Perform dilated funduscopic examination
16. Verify that patient meets all entry criteria

13.2.1. Patient Instructions

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.1.2](#) .

13.3. Visit 3/Day 1/Dosing/Treatment, Cohort 3

Query patient about changes in medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

13.3.1. Pre-dose Assessments

Assessments will be conducted in the following general order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction

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2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at between 6:00 a.m. and 10:00 a.m. (± 30 minutes)
 - a. IOP must be between 22-34 mm Hg in both eyes with a ≤ 4 mm Hg difference between each eye at 8:00 a.m. (± 30 minutes)
 - b. IOP must increase of at least 4 mmHg in each eye compared to the pre-washout baseline
5. Perform gonioscopy
6. Instill one drop of VIGAMOX into the study eye
7. Verify that patient meets all entry criteria

13.3.2. Study Eye Assignment and Study Drug Administration

Patients will be assessed to ensure they still qualify to participate in the study based on the inclusion/exclusion criteria ([Section 11.3](#) and [Section 11.4](#)). The patient's study eye will be assigned to receive one or two ENV515-3-2 (travoprost) Intracameral Implant(s) into the study eye via intracameral injection administered via the provided intracameral implant applicator. The study-trained investigator will administer the dose of study medication into the study eye (see [Section 14.1.1](#), Implantation of ENV515) between 6:00 a.m. and 10:00 a.m. (± 30 minutes). Timolol maleate 0.5% ophthalmic solution will be administered into the non-study eye by the patient at 8 p.m. (± 60 minutes) on the day of Visit 3.

13.3.3. Post-dose Assessments

1. Perform slit lamp biomicroscopy
2. Dispense bottle of timolol maleate 0.5% ophthalmic solution to the patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~12:00 p.m.); however, at the discretion of the investigator, patients will be permitted to leave the clinic following the completion of the dosing.

13.3.4. Patient Instructions

Before patients leave the clinic, they should receive an appointment for their next study visit and the following instructions:

- Remember to use timolol maleate 0.5% ophthalmic solution twice daily (as close to 8:00 a.m. and 8:00 p.m. as you can ± 60 minutes) in the non-study eye. **DO NOT PUT** timolol maleate 0.5% ophthalmic solution in the eye that received the ENV515 implants. Continue using timolol maleate 0.5% ophthalmic solution until one day prior to Visit 16 (Month 12 ± 7 days). Please remember to bring timolol maleate 0.5% ophthalmic solution with you at each subsequent visit so that it can be

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administered after the 8:00 a.m. IOP measurement. It will need to be collected from you before issuing a new bottle at applicable visits.

- Continue to withhold (not use) all other eye drop medications until the end of the study (if appropriate). With your investigator's approval, you may be able to use artificial tear eye drops.
- Remember not to wear contact lenses.
- Please avoid physical activities associated with jarring physical motions, such as horseback riding, for the rest of the study.
- Call your study site if you have any problems.

13.4. Visit 4/Day 2 + up to 3 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
5. Perform gonioscopy
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only; Non-contact specular microscopy can be performed anytime during the site visit

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~10:00 a.m.).

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.5. Visit 5/Day 14 \pm 3 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

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Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study)
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4:00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) study eye only; Non-contact specular microscopy can be performed anytime during the site visit
9. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
10. Measure IOP at 10:00 a.m. (± 30 minutes)
11. Measure IOP at 4:00 p.m. (± 30 minutes)
12. Collect blood sample for PK analysis. (can be performed after the 10 a.m. IOP)

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.6. Visit 5a/Day 28 \pm 3 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy (If corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.

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5. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4:00 p.m. IOP measurement)
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only; Non-contact specular microscopy can be performed anytime during the site visit
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
9. Measure IOP at 10:00 a.m. (± 30 minutes)
10. Measure IOP at 4:00 p.m. (± 30 minutes)
11. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient
12. Collect blood sample for PK analysis (can be performed after the 10 a.m. IOP)

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.7. Visit 6/Day 42 \pm 3 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy (If corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
3. Perform corneal staining
4. Measure IOP at 8:00 a.m. (± 30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
5. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only; Non-contact specular microscopy can be performed anytime during the site visit
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image

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9. Measure IOP at 10:00 a.m. (± 30 minutes)
10. Measure IOP at 4:00 p.m. (± 30 minutes)
11. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient
12. Collect blood sample for PK analysis (can be performed after the 10 a.m. IOP)

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.8. Visit 7/Day 84 \pm 7 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise noted:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy (If corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (± 30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) study eye only; Non-contact specular microscopy can be performed anytime during the site visit
9. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
10. Measure IOP at 10:00 a.m. (± 30 minutes)
11. Measure IOP at 4:00 p.m. (± 30 minutes)
12. Perform body system assessment (can be performed anytime during the site visit)
13. Assess vital signs (can be performed anytime during the site visit)
14. Perform dilated fundus exam

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15. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed after the 10:00 a.m. IOP)
16. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.9. Visit 8/Month 4 – Visit 12/Month 8 ± 7 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform pupil measurement
3. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites)
4. Perform corneal staining
5. Measure IOP at 8:00 a.m. (±30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
6. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 4 :00 p.m. IOP measurement)
7. Perform pachymetry (contact)
8. Perform specular microscopy (non-contact) study eye only (can be performed anytime during the site visit)
9. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
10. Measure IOP at 10:00 a.m. (±30 minutes)
11. Measure IOP at 4:00 p.m. (±30 minutes)
12. Perform body system assessment (can be performed anytime during the site visit) only at **Visit 10 (Month 6) and Visit 13 (Month 9)**
13. Assess vital signs (can be performed anytime during the site visit) only at **Visit 10 (Month 6) and Visit 13 (Month 9)**

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14. Perform dilated funduscopy examination only at **Visit 10 (Month 6) and Visit 13 (Month 9)**
15. Collect non-fasting blood and urine for clinical laboratory tests at Month 6 (Visit 10) (should be performed any time after the 10:00 am IOP measurement)
16. Collect systemic PK at all visits (should be performed any time after the 10:00 am IOP measurement)
17. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures (~7:30 a.m. to ~5:00 p.m.). However, at the discretion of the investigator, patients will be permitted to leave the clinic after completing the 10:00 a.m. IOP measurement and will return to the clinic before the 4:00 p.m. IOP measurement. Any patient that leaves the clinic will be instructed to return no later than 30 minutes prior to the 4:00 p.m. IOP measurement.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.10. Visit 13/Month 9 – Visit 15/Month 11 ± 7 Days/Treatment Period, Cohort 3

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites)
3. Measure IOP at 8:00 a.m. (±30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
4. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
5. Perform pachymetry (contact)
6. Perform specular microscopy (non-contact) study eye only (can be performed anytime during the site visit)
7. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image

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8. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures. Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 13.3.4](#).

13.11. Visit 16/Month 12 \pm 7 Days/Treatment Period Study Exit, Cohort 3 (if patient chooses not to enroll in Cohort 3 Extension 1)

The following procedures are to be performed during an exit visit or during an early exit visit if a patient discontinues prior to Visit 16 (Month 12).

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
3. Measure IOP at 8 am (\pm 30 minutes) - Please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement.
4. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
5. Perform pachymetry (contact)
6. Perform specular microscopy (non-contact), can be performed anytime during the site visit
7. Assess VF
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
9. Perform dilated funduscopy exam
10. Perform body system assessment (can be performed anytime during the site visit)
11. Assess vital signs (can be performed anytime during the site visit)
12. Collect non-fasting blood and urine for clinical laboratory tests **and** systemic PK (can be performed any time after the 10 a.m. IOP)
13. If female of childbearing potential, perform urine pregnancy test

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14. Collect used timolol maleate 0.5% ophthalmic solution bottle
15. Complete the exit page in eCRF
16. Discharge the patient from the trial

13.12. Visit 16/Month 12 – Visit 21/Month 17 ± 7 Days/Treatment Period, Cohort 3 Study Extension 1 (if patient chooses to enroll in Cohort 3 Extension 1)

Obtain written consent to participate in Cohort 3, Extension 1 before any study extension related activities begin.

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Obtain written informed consent before or at Visit 16/Month 12 to participate in Cohort 3 Extension 1
2. Assess BCVA (ETDRS) with manifest refraction
3. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
4. Measure IOP at 8:00 a.m. (±30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
5. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
9. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

13.13. Visit 22/Month 18 \pm 7 Days/Treatment Period Study Exit, Cohort 3 Study Extension 1 (if patient chooses not to enroll in Cohort 3 Extension 2)

The following procedures are to be performed during an exit visit or during an early exit visit if a patient discontinues prior to Visit 22 (Month 18).

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
3. Measure IOP at 8 a.m. (\pm 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
4. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
5. Perform pachymetry (contact)
6. Perform specular microscopy (non-contact) for both eyes (can be performed anytime during the visit)
7. Assess VF
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
9. Perform dilated funduscopy exam
10. Perform body system assessment (can be performed anytime during the site visit)
11. Assess vital signs (can be performed anytime during the site visit)
12. Collect non-fasting blood and urine for clinical laboratory tests
13. If female of childbearing potential, perform urine pregnancy test
14. Collect used timolol maleate 0.5% ophthalmic solution bottle
15. Complete the exit form
16. Discharge the patient from the trial

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13.14. Visit 23/Month 19 – Visit 27/Month 23 ± 7 Days/Treatment Period, Cohort 3 Study Extension 1 (if patient chooses to enroll in Cohort 3 Extension 2)

Obtain written consent to participate in Cohort 3, Extension 2 before any study extension related activities begin.

Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Obtain written informed consent before or at Visit 16/Month 12 to participate in Cohort 3 Extension 2
2. Assess BCVA (ETDRS) with manifest refraction
3. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
4. Measure IOP at 8:00 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
5. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
6. Perform pachymetry (contact)
7. Perform specular microscopy (non-contact) study eye only
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
9. Collect used timolol maleate 0.5% ophthalmic solution bottle and distribute new bottle to patient

Patients are expected to remain in the clinic for the completion of all procedures.

Before patients leave the clinic, they should receive an appointment for their next study visit and the instructions provided in [Section 12.3.4](#).

13.15. Visit 28/Month 24 ± 7 Days/Treatment Period Study Exit, Cohort 3 Study Extension 2

The following procedures are to be performed during an exit visit or during an early exit visit if a patient discontinues prior to Visit 28 (Month 24).

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Query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Assessments will be conducted in the following order. Both eyes will be evaluated at all ophthalmic assessments unless otherwise indicated:

1. Assess BCVA (ETDRS) with manifest refraction
2. Perform slit lamp biomicroscopy (if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
3. Measure IOP at 8 a.m. (± 30 minutes, please make sure that timolol maleate 0.5% ophthalmic solution is administered after the IOP measurement)
4. Perform gonioscopy (if gonioscopy images are collected, please conduct the gonioscopy after the 8:00 a.m. IOP measurement)
5. Perform pachymetry (contact)
6. Perform specular microscopy (non-contact) for both eyes (can be performed anytime during the visit)
7. Assess VF
8. Perform anterior chamber OCT with the ENV515 implant(s) in the field of view of at least one OCT image
9. Perform dilated funduscopy exam
10. Perform body system assessment (can be performed anytime during the site visit)
11. Assess vital signs (can be performed anytime during the site visit)
12. Collect non-fasting blood and urine for clinical laboratory tests
13. If female of childbearing potential, perform urine pregnancy test
14. Collect used timolol maleate 0.5% ophthalmic solution bottle
15. Complete the exit form
16. Discharge the patient from the trial
- 17.

13.16. Unscheduled Visits, Cohorts 2 and 3

Patients may need to be seen at other times than the scheduled study visits for additional safety assessments or to follow-up, as medically necessary, on changes in clinical status or to follow-up on clinical laboratory or other findings. If an additional study visit occurs, the date and nature of the visit will be documented.

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During unscheduled visits, query patient about changes in concomitant medications and whether or not they have experienced symptoms suggesting an AE. AEs and concomitant medications will be documented.

Mandatory assessments will be conducted in the following order. Only study eye will be evaluated at the listed ophthalmic assessments, with additional evaluations carried out as deemed necessary per the investigator's discretion:

1. Perform slit lamp biomicroscopy (If corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
2. Assess BCVA (ETDRS) with manifest refraction
3. Measure IOP at 8:00 a.m. (± 30 minutes) or when feasible
4. Perform pachymetry (contact)
5. Perform specular microscopy (non-contact), can be performed anytime during the site visit
6. Adverse Event assessment
7. Concomitant medication assessment

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14. TREATMENT OF PATIENTS, COHORTS 2 AND 3

14.1. Treatments to be Administered, Cohorts 2 and 3

14.1.1. Implantation of ENV515, Cohorts 2 and 3

Treatment will consist of a single intracameral injection of low dose ENV515-3 (travoprost) Intracameral Implants in Cohort 2, and a single intracameral injection of low or high dose of ENV515-3-2 (travoprost) Intracameral Implants in Cohort 3 into the study eye, defined as the qualifying eye with higher mean diurnal IOP during the Baseline Visit or the left eye if both eyes have the same mean diurnal IOPs at the Baseline Visit. The study eye will be selected during the Dosing Visit (Visit 3). All investigators will be trained in implant loading, administration, and retrieval (if necessary) by Envisia. Timolol maleate 0.5% ophthalmic solution will be administered into the non-study eye once on Day 1 at 8:00 p.m. Starting on Day 2 patients will administer timolol maleate 0.5% ophthalmic solution twice a day (8 a.m. and 8 p.m. ± 60 minutes) until the night prior to Visit 16 (Month 12) in the non-study eye.

ENV515-3 and ENV515-3-2 (travoprost) Intracameral Implants will be supplied in sterile glass vials with 1 implant per vial. The sterile implant applicator will be provided in a Tyvek[®] pouch. The packaging will be opened and the implant applicator and the implants will be placed into a sterile field. Implants will be loaded into the implant applicator by the trained investigator or trained Envisia staff member immediately prior to dosing. Additionally, the study eye will be administered 3 doses of topical antibiotic VIGAMOX: first dose following the completion of the pre-dose assessments ([Section 12.3.1](#) and [Section 13.3.1](#)) and immediately before and after the ENV515 implant administration as described below. The following instructions will be minimally distributed with the ENV515 implants and implant applicator:

Opening Instructions, Cohorts 2 and 3

1. Use sterile technique in sterile field to open primary packaging for the applicator and ENV515 implants.
2. Open ENV515 Implant Applicator packaging and place the sterile ENV515 applicator into sterile field.
3. Do not open glass vial containing implants until ready to load into the applicator.

Instructions for Loading the Implant into the Applicator by the Investigator, Cohorts 2 and 3

1. Load two ENV515-3 implants in Cohort 2, and one or two ENV515-3-2 implant(s) in Cohort 3 into the ENV515 Implant Applicator in a sterile field using sterile technique via insertion through the beveled needle end.

Instructions for Administration by Principal Investigator, Cohorts 2 and 3

1. Instill second dose of VIGAMOX into the study eye (first dose is administered during ocular exams)

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2. Treat patient's ocular surface with topical anesthetic (proparacaine 0.5% or equivalent).
3. Treat patient's ocular surface with 5% povidone iodine and wait 2 minutes.
4. Insert lid speculum.
5. Administer the implant(s) into the anterior chamber via intracameral injection through clear, peripheral cornea. The needle should be advanced parallel with the iris, ~1 mm anterior to the limbus with the patient sitting at the slit lamp, or with the patient supine under the operating scope.
6. Instill third dose of VIGAMOX into the study eye.

One implant applicator and 4 glass vials with 1 ENV515-3 or 5 glass vials with 1 ENV515-3-2 implant/vial will be packaged in appropriately labeled cartons in Cohorts 2 and 3, respectively. The label on the package will minimally contain the following information: each package contains no less than 4 glass vials with 1 ENV515-3 or 5 glass vials with 1 ENV515-3-2 implant/vial, 1 ENV515 implant applicator; study ENV515-01, storage temperature, and "Caution: Limited by Federal (or United States) Law to Investigational use." An unmasked disclosure panel will be displayed on the bottle label of the study medication and will minimally contain the following information: ENV515-01, and name of product. The study medications will be stored in a secure area with limited access to study personnel under refrigerated storage at approximately 2 to 8°C.

14.1.2. Timolol maleate 0.5% Ophthalmic Solution for Non-Study Eye, Cohorts 2 and 3

Timolol maleate 0.5% ophthalmic solution will be provided for the non-study eye with its original packaging, labeling, and instructions for use (non-study eye only).

15. PROCEDURE DESCRIPTION

15.1. Measurements and Evaluations, Cohorts 1, 2 and 3

15.1.1. Best-Corrected Distance VA With Manifest Refraction Guidelines

VA will be measured using the ETDRS chart. VA should be taken with the patient's best-correction for distance at designated visits (method of correction should be consistent across visits). It is important to take time for careful refraction of those patients with reduced VA. Spectacle correction is not allowed. A consistent distance to the chart and method of measurement should be used throughout the trial. The VA will be measured in the following way.

1. When performing visual acuities it is recommended that the lighting should be at approximately office levels, be approximately uniform between the patient and the chart, and is used consistently the same way throughout the trial.
2. For manifest refraction, use "Chart R." For actual vision testing, use "Chart 1" for the right eye and "Chart 2" for the left eye.
3. The technician should ask the patient to read each letter slowly from the top of the chart and down as far as possible. Do not point to letters.
4. The patient should try no longer than 1 minute to see any 1 line. If the patient has difficulty reading a letter, they should be encouraged to guess. When the patient can read no further, the technician should ask the patient twice to read to the line below where the last correct letter was recognized. When a letter is read correctly, the examiner will record this on a score sheet with a layout identical to that of the chart.
5. The total number of letters missed will be recorded on the worksheet and entered in the eCRF.

To record the Logarithm of the Minimum Angle of Resolution (LogMAR) VA:

- Record the last line from which at least one letter is read correctly; this is the Base LogMAR.
- Record the total number of letters missed.

15.1.2. Slit Lamp Biomicroscopy Exam Guidelines

Slit lamp biomicroscopy will be performed using the investigator's standard procedure. This procedure will be the same for all patients observed at an investigator's site. Observations should be graded as normal or abnormal. In the event of abnormal observations, all findings should be noted and specified as clinically significant or not clinically significant and graded on a 5 point scale (0 = None, 0.5 = Trace, 1.0 = Mild, 2.0 = Moderate, 3.0 = Severe). Observations for each eye should be made of the following variables:

- Eyelid erythema

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- Chemosis
- Corneal Staining
- Corneal edema
- Corneal opacity (At Visit 2 (Baseline) and if corneal opacity is observed, please collect corneal photograph at each visit until opacity has resolved or patient is exited from the study at selected sites.)
- Hyphema
- Anterior synechiae
- Posterior synechiae
- Lens
- Conjunctival hyperemia (Hyperemia should be evaluated on a seven point scale [0, 0.5, 1, 1.5, 2, 2.5, 3] against the provided Ora Calibra™ Redness Scale #6.0b. Findings should be noted as diffuse or injection site).
- Conjunctiva (findings other than hyperemia)

Anterior Chamber Cells Grading Scale – evaluated against the SUN Scale (9)

0 = <1 cell in field

.5+ = 1-5 cells in field

1+ = 6-15 cells in field

2+ = 16-25 cells in field

3+ = 26-50 cells in field

4+ = 50+ cells in field

Anterior Chamber Flare Grading Scale - evaluated against the SUN Scale (9)

0 = None

1+ = Faint

2+ = Moderate (Iris/lens details clear)

3+ = Marked (Iris/lens details hazy)

4+ = Intense (fibrin/plastic aqueous)

15.1.3. Corneal Staining

The cornea will be stained with non-preserved 2% fluorescein. When conducting all assessments room temperature and humidity should be relatively consistent throughout each visit and throughout the study. Observations should be graded as normal or abnormal. In the event of

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abnormal observations, all findings should be noted and specified as clinically significant or not clinically significant and graded for severity on a 0-5 scale.

15.1.4. Binocular Indirect Ophthalmoscopy (Dilated Fundus Exam) Guidelines

Dilated ophthalmoscopy will be performed according to the investigator's preferred procedure. This procedure will be the same for all patients observed at an investigator's site. Observations should be graded as normal or abnormal. All findings should be noted and specified as clinically significant or not clinically significant and graded for severity on a 0 - 5 scale. The fundus will be examined thoroughly and the following variables examined:

- Retina
- Macula
- Choroid
- Vitreous
- Optic nerve/disc
- Cup/disc ratio

15.1.5. Body System Review

Abbreviated body system review examinations will be performed and include the following examinations.

- General appearance
- Skin
- Lymphatic
- Head and Neck
- Ears Nose and Throat
- Chest and Lungs
- Cardiovascular
- Abdomen
- Extremities
- Musculoskeletal
- Neuromuscular

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15.1.6. Vital Signs

Vital sign assessments will include measurements of heart rate, blood pressure, and respiration rate.

15.1.7. Laboratory Safety Assessments and Systemic Exposure to Travoprost

Laboratory samples will be collected as indicated in the Times and Events schedules. Labs should be non-fasting however, if not, please indicate on the lab requisition form as well as in the patient's chart. Chemistry, hematology and urinalysis will be assessed according to the central laboratory procedures manual. A urine pregnancy test will be performed on all females of childbearing potential.

15.1.8. Anterior Chamber Optical Coherence Tomography (OCT)

Anterior chamber OCT images will be acquired per instructions provided in the OCT manual. Images will be evaluated for angle opening distance at a central reading center. Additional details about collection, handling and interpretation of images will be provided in the OCT manual. At least one collected anterior chamber OCT image should include the ENV515 implant(s) in the field of view at each visit.

15.1.9. Gonioscopy

Gonioscopy will be performed to grade the iridocorneal angle according to the Shaffer gonioscopy scale. Gonioscopy will also be used to monitor the implant location. The Shaffer scale should be used to describe the angle created between the plane of the iris and the cornea as follows:

- Grade 4: 35 to 45 degrees, wide open, closure improbable
- Grade 3: 20 to 35 degrees, moderately narrow, closure possible
- Grade 2: <20 degrees, extremely narrow, closure probable
- Grade 1: partly or totally closed, closure present

The orientation of the implants will need to be indicated on source documents for each patient. In Cohorts 2 and 3 select sites will collect gonioscopy images. If gonioscopy images are collected, please conduct the gonioscopy after the last IOP measurement. Photographs will be taken at visits post dose starting a Visit 5 and continue at visits until the patient is exited from the study.

15.1.10. Visual Field (Humphrey Program 24-2 SITA-Standard Strategy)

The VF assessment will be performed on the Humphrey Field Analyzer using the program 24-2. All VF examinations will be performed with the patient's best correction for 33 cm. The pupil should be at least 3 mm in diameter. If not, pharmacologic dilation should be used for VF testing. Quantified single threshold perimetry may be used if desired. Swedish Interactive Threshold Algorithms (SITA), Fastpac, or a similar program may be used. SITA Fast may not be used.

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15.1.11. Intraocular Pressure

All IOPs will be measured with a Goldmann applanation tonometer. The calibration of the tonometer will be checked at least monthly and recorded in a log. Diurnal curves will be recorded at specified visits. The time of tonometry will be recorded on the source document for all visits.

IOP should be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. Measurements will be taken by two qualified independent study site personnel using a Goldmann applanation tonometer affixed to a slit lamp with the patient seated. One person will adjust the dial in masked fashion and a second person will read and record the value. The patient and slit lamp should be adjusted so that the patient's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Both eyes will be tested, with the right eye preceding the left eye. Each IOP measurement is to be recorded.

One person ("the measurer") looks through the binocular viewer of the slit lamp at low power. The tension knob is pre-set at a low pressure value (4 to 6 mmHg). The measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the measurer takes his/her fingers off the tension knob and the second person ("the reader") records the IOP reading along with the date and time of day in the source document, thus maintaining a masked IOP reading.

For Cohorts 1 and 2, three consecutive measurements will be taken to determine IOP in the manner described above. All three measurements will be recorded and the median IOP of the three measurements will be recorded and used in the analysis.

For Cohort 3, only two measurements are necessary if the pressure measurements are the same. If the two measurements are not identical, a third measurement is required.

15.1.12. Pachymetry (Contact)

Following IOP measurements, the central corneal thickness of each eye will be measured with the patient seated and visualizing fixation.

An ultrasonic pachymeter equipped with a solid tip probe must be used.

Center the probe tip on the cornea and take a measurement when it is correctly positioned. Obtain 3 measurements (displayed in microns) for each eye and average the values to obtain the corneal thickness measurement.

15.1.13. Specular Microscopy (Non-contact)

Perform assessment according to the manufacturer's specified instructions. The image analysis will be conducted by centralized reading center. Detailed instructions for submission of images will be provided in a manual from the reading center.

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For Cohort 2, specular microscopy is needed for all study eyes on Visits 1 through 10, 12, 14, and 16. For non-study eyes, it is collected only during Visits 1 and 16 for Cohort 2. Cohort 3 requires for non-study eyes images to be collected at Visits 1 and 2. Non-contact specular microscopy can be performed anytime during the study visit.

15.1.14. Pupil Measurement

Pupil diameter will be measured in a room (not at the slit lamp) with lighting that is used consistently the same way throughout the trial. Instruct the patient to gaze into the distance, and then compare the pupil diameter to a standardized schematic. A standardized schematic will be provided by the sponsor.

15.1.15. Implant Recovery and Aqueous Humor Sampling

In Cohort 1, the cataract surgery and intraocular lens (IOL) implantation will be conducted according to the discretion of the principal investigator per established protocols. The implant removal will be conducted during the cataract surgery. The implant removal procedure as described below was used in nonclinical studies of ENV515. Based on observations in nonclinical studies of ENV515 in Beagle dogs, the implants retain their original size and shape, do not disintegrate for at least 2 months in situ at the iridocorneal angle in vivo, and do not disintegrate when manipulated via instruments such as utrata forceps after 2 months in situ in vivo. The following study-specific procedures will be performed during the cataract surgery:

1. The implant location(s) are identified by gonioscopy exam conducted during pre-surgery assessments.
2. Following the creation of the initial incision in the clear cornea, ~100 μ L of aqueous humor will be sampled from the anterior chamber via provided tuberculin syringe with 30 gauge needle. The sample will be treated as described in [Appendix 1](#).
3. After the removal of the aqueous humor sample, implants will be recovered from the anterior chamber.
4. A stream of buffered saline solution (BSS) is directed to the iridocorneal angle location where the implants have been identified until implants are dislodged from the iridocorneal angle and float in the anterior chamber. Utrata forceps or equivalent instrument is used to grasp the implant and remove the implant(s) through the incision in the clear cornea created for cataract removal and IOL implantation.
5. Recovered implants will be treated as described in [Appendix 1](#).

In Cohorts 2 and 3, patients are not scheduled for cataract surgery. However, steps 1 through 5 can be used to remove implants if absolutely necessary.

15.2. Stopping Rules

15.2.1. Stopping Rules for the Study

The medical monitor will evaluate safety data (e.g. AE reports) on a regular basis. Consultation with the principal investigators will occur as appropriate.

The trial or parts of the trial may be discontinued by Envisia at the recommendation of the medical monitor. This may be based on a significant number of AEs of a similar nature that warrant such action. The medical monitor may request at any time a meeting with the Envisia project team for the purposes of conducting a full evaluation of safety. This evaluation may result in a recommendation by the medical monitor to Envisia to terminate the study. If the medical monitor recommends to Envisia to terminate the study, Envisia will evaluate the recommendation, and make a decision whether to continue the study, make any changes to the study including but not limited to stopping further dosing, or discontinue the study. An Envisia representative will inform the FDA, the medical monitor, and all participating clinical sites and their principal investigators of the medical monitor's recommendation and Envisia decision within 48 hours from the recommendation to stop the study.

In the event that study discontinuation is necessary (i.e. no more patients are being dosed), the investigator should make every attempt to complete all protocol safety assessments and visits for patients who have been dosed in Cohorts 2 and 3. For Cohort 1, the cataract surgery combined with the removal of the implant(s) should occur as soon as possible based on the judgment of the investigator and safety of the patient. Unless consent has been withdrawn, any patient is considered to be in the treatment phase of the study until the cataract surgery combined with ENV515 implant removal, and such patients should continue to be followed and will be expected to complete all pre- and post- surgery safety assessments and visits for Cohort 1 or until study is completed for Cohorts 2 and 3.

16. WASHOUT MEDICATIONS, CONCOMITANT MEDICATIONS, DRUG ACCOUNTABILITY, AND MAINTENANCE OF RANDOMIZATION

16.1. Washout Medications

During the Screening Visit, patients will be asked to discontinue their current glaucoma medication(s), for the appropriate time period. The patient will be asked to return for the Baseline Visit within 4 weeks for Cohorts 1 and 2. Patients will be scheduled to return for an interim IOP check if their washout period will be longer than 4 weeks. The washout period will be extended up to 2 additional weeks (if medically safe) to accommodate the patient's or investigator's schedule. Patients will be washed out for 6 weeks for all glaucoma medications in Cohort 3. Patients should discontinue the use of any glaucoma medication(s) with the exception of study medication for the duration of the study.

16.2. Concomitant Medications

16.2.1. Permitted Medications

Medications permitted include systemic medications with the exception of oral, ocular, or IV steroids. Only non-preserved artificial tears will be allowed to be administered as an ocular treatment. Medications not specifically excluded in [Section 16.2.2](#) may be taken as necessary.

The use of topical non-steroidal anti-inflammatory agents (e.g. PROLENSA, ACULAR, ILEVRO or others) is allowed per the discretion of the investigator for 1 to 2 days prior to and 7 days immediately following ENV515-3-2 administration via intracameral injection.

All medications taken by a patient 30 days prior to Visit 1 through the end of the study will be recorded in the eCRF and the patient's medical chart. **This includes all ocular medications given on the day of dosing.** The generic name (if known, otherwise the trade name) of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, and indication will be recorded for each medication.

Topical medications that are administered to all patients as part of conducting safety assessments or routine procedures are not required to be recorded in the eCRF. For example, topical medications used for the following are not required to be recorded in the eCRF:

- Dilating agents
- Anesthesia
- Staining (i.e., fluorescein)

16.2.2. Medications Not Permitted

The use of medical marijuana and corticosteroids (oral, ocular, injectable, or IV) are disallowed with the exception of inhaled, intranasal or topical (dermal) steroids if on a stable dose.

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In the event that a subject requires the initiation of one or more of these medications during the study, the investigator must consult with the sponsor regarding the proper action that should be taken.

16.3. Investigational Product Accountability

Investigational product (IP), including the provided injectors, will not be shipped to any investigational site until the site has fulfilled all requisite regulatory requirements. Accountability of IP, ENV515 and TRAVATAN Z for the non-study eye in Cohort 1 and ENV515 and timolol maleate 0.5% ophthalmic solution for Cohorts 2 and 3, will be conducted by the Envisia monitor or designee. Accountability will be ascertained by performing reconciliation between the amount of drug sent to the site, the amount used and the amount unused at the time of reconciliation.

Clinical trial materials will be shipped to the investigational sites under sealed conditions. IP shipment records will be verified by comparing the shipment inventory sheet to the actual quantity of drug received at the site. Accurate records of receipt and disposition of the study drug (e.g., dates, quantity, patient number, dose dispensed, returned, etc.) must be maintained by the investigator or his/her designee. IP will be stored under refrigerated storage at approximately 2 to 8°C. This area should be limited controlled access.

Patient's compliance with administration of the control arm medication (TRAVATAN Z or timolol maleate 0.5%) will be assessed by the site staff upon return of the study medication to the site. If bottle(s) were unopened or clearly unused between visits or if the patient reports a significant time frame of 5 or more days of not using their control arm medications prior to the study visit, a note should be made in the drug accountability log, in the patient's source document (patient chart) and in the eCRF.

At the end of the study, all study materials, including used and unused study drug (ENV515, TRAVATAN Z and timolol maleate 0.5%) are to be returned to Envisia (or designee) or destroyed under the direction of the same. The removed implants will be retained per instructions in [Appendix 1](#). The study monitor or designee will verify drug accountability. All drug accounting procedures must be completed before the study is considered complete.

16.4. Maintenance of Randomization

For Cohort 1, a randomization code for the patient assignment to 1 of 4 dose levels of ENV515 will be computer-generated by either Envisia or its designee. Randomization team members will work independently of other team members. Study personnel, study patients, and project teams at Envisia, the medical monitor, and the CRO involved in the study will be unmasked to treatment assignments. To randomize a patient (Visit 3), the investigator (or designee) will confirm in the eCRF that the patient remains qualified for the study. The eCRF will automatically assign the dose and number of implants that the patient should receive based on a prospectively prepared computer generated code list.

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In the event of a medical need during Cohort 1, the investigator treated each patient as needed. The study design allowed for removal of the ENV515 intracameral implant by scheduling the subject for cataract surgery at an earlier date as determined by the medical need during which the ENV515 implant(s) was/were removed.

For Cohorts 2 and 3, no randomization was conducted as these are open-label, single arm cohorts.

17. SAFETY REPORTING

17.1. Adverse Events Reporting

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. AEs will be monitored throughout the study and will be recorded on the eCRF with the date and time of onset, date and time of resolution, intensity, seriousness, causality (relationship to study medication), and treatment required. From point of consent but prior to dosing, AEs and SAEs are classified as Medical Event.

To elicit AEs, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the trial. For example:

- How have you felt since your last assessment?
- Have you had any health problems since your last assessment?

The severity of each AE should be categorized as mild, moderate, or severe. Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the patient. The assessment of severity is made irrespective of relationship to investigational product or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the patient, but is easily tolerated and does not interfere with the patient's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

The causality of the study treatment in relation to the AE will be assessed by the principal investigator after careful medical consideration and categorized as not related, possibly related, or related.

The expectedness of each AE should be determined based upon existing safety information about the investigational product using these explanations:

- *Unexpected*: An AE that is not listed in the IB or Report of Prior Investigations (ROPI) or is not listed at the specificity or severity that has been observed.
- *Expected*: An AE that is listed in the IB at the specificity and severity that has been observed.
- *Not applicable*: An AE unrelated to the investigational product.

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The relationship of each AE to the investigational product and the administration procedure should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the investigational product caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the investigational product caused the AE.

For Cohorts 2 and 3, causality of AEs were further assessed using the following selections:

- Unrelated to any study procedure or any study medications
- ENV515 implant
- Comparator
- Injection Procedure
- Other study procedure(s)

Suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure; one or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed to the investigational product; an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational product-treatment group than in a concurrent or historical control group.

AEs that are mentioned in the Investigator’s Brochure occurring with a class of products or as anticipated from the pharmacological/ mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected. The sponsor will classify the expectedness of an AE with a final review by the Medical Monitor.

If an AE occurs, the investigator will institute support and/or treatment as deemed appropriate. If a serious or treatment-related AE is unresolved at the time of the last day of the study, an effort will be made to follow up until the AE is resolved or stabilized, the patient is lost to follow-up, or there is some other resolution of the event. The investigator should make every attempt to follow SAEs to resolution.

17.2. AEs of Special Interest and Their Reporting

An adverse event of special interest (AESI) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. AESIs for the this study include any corneal events including corneal edema detected via slit lamp or pachymetry, corneal opacity, and any suspected changes in corneal endothelial cell counts determined by the central reading center of 30% or greater change from baseline (V2) as determined via specular microscopy.

If AESI of corneal edema or corneal opacity occur, the investigators or their designees should report all such AESIs to Envisia within 24 hours of the event being brought to the investigators' or their staffs' attention. Should any decrease in corneal endothelial cell count equal or greater than 30% change from study baseline occur, the investigators will be promptly notified by the Envisia team and/or the centralized reading center.

17.3. Prospective Definitions of Select AEs

Selected events are classified further via the use of a prospective AE definition to provide investigators additional medically relevant considerations and to improve patient safety. Such definitions are provided below for this study:

Adverse Event of Corneal Endothelial Cell Loss: Any decrease in corneal endothelial cell count equal or greater than 30% change from study baseline count of corneal endothelial cells (Visit 2, Study Baseline) is considered an adverse event. The corneal endothelial cell counts are evaluated via an independent centralized reading center. Should any decrease in corneal endothelial cell count equal or greater than 30% change from study baseline occur, the investigators will be promptly notified by the Envisia team and/or the centralized reading center.

Additional medically relevant considerations are provided for the classification of mild, moderate and severe instances for AE of corneal endothelial cell loss:

- Mild AE of corneal endothelial cell loss: patient's corneal endothelial cell counts are in the range from greater than 1,200 cells/mm² to less than or equal to 30% change from baseline (dependent on individual patient's baseline)
[1,200 cells/mm² < mild AE cell count ≤ 30% change from patient's baseline]
- Moderate AE of corneal endothelial cell loss: patient's corneal endothelial cell counts are in the range from greater than 900 cells/mm² to less than or equal to 1,200 cells/mm²
[900 cells/mm² < moderate AE cell count ≤ 1,200 cells/mm²]
- Severe AE of corneal endothelial cell loss: cell counts are in the range of greater than 600 cells/mm² to less than or equal to 900 cells/mm²
[600 cells/mm² < severe AE cell count ≤ 900 cells/mm²]

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Any corneal endothelial cell loss leading to cell counts at or below 600 cells/mm² should be classified as Serious Adverse Event (SAE, see [Section 17.5](#) for additional medically relevant considerations for classifying a corneal endothelial cell loss as SAE).

17.4. Serious Adverse Event Reporting

It is the responsibility of the investigators or their designees to report any SAE to Envisia within 24 hours of the event being brought to the investigators' or their staffs' attention. It is also the responsibility of the investigator to report all SAEs reported at their site to their Institutional Review Board (IRB), as required. If an unexpected SAE, determined to be related or possibly related to study medication occurs in any study involving ENV515, all sites will be notified by Envisia and they should report it to their IRB. The investigator should make every attempt to follow all SAEs to resolution.

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse drug experience (i.e., the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred);
- inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect; or
- other important medical events not meeting the above criteria that, based on appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes.

The following information should be provided when an SAE is reported to Envisia:

1. Protocol number
2. Site number
3. Patient initials
4. Patient number
5. Patient demographic information, including:
 - Date of birth
 - Sex
 - Race

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6. Study drug start date (TRAVATAN Z and ENV515 implant date for Cohort 1, timolol maleate 0.5% ophthalmic solution for Cohorts 2 and 3, ENV515-3 for Cohort 2 and ENV515-3-2 for Cohort 3)
7. Date of last dose of TRAVATAN Z or ENV515 implant removal date for Cohort 1 and date of the last dose of timolol maleate 0.5% ophthalmic solution for Cohorts 2 and 3
8. SAE information, including:
 - Description of SAE/narrative
 - Diagnosis only (if known) or serious signs/symptoms
 - Date/time of onset
 - Frequency
 - Severity
 - Date/time of resolution or death (if duration <24 hours)
 - Relationship to study drug
 - Action taken
9. Criteria for classifying the event as serious, including whether the SAE resulted in any of the following:
 - Death
 - Life-threatening
 - Disabling or incapacitating
 - Hospitalization required or prolonged
 - Congenital anomaly
 - Other - investigator must specify
10. Concomitant medications
11. Relevant history
12. Copy of the Adverse Event page from the eCRF

17.5. Additional Medically Relevant Considerations for Defining Corneal Endothelial Cell Loss as an SAE

Serious Adverse Event of Corneal Endothelial Cell Loss: If an event meets any of the three criteria described below, it is considered a serious adverse event of corneal endothelial cell loss. Should any decrease in corneal endothelial cell count equal or greater than 30% change from study baseline occur, the investigators will be promptly notified by the Envisia team and/or the centralized reading center.

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AE of corneal endothelial cell loss is considered “serious” (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Corneal endothelial cell loss occurs that results in a cell count ≤ 600 cells/mm²
- Corneal endothelial cell loss of $\geq 70\%$ that results in persistent change in BCVA of three lines of vision (15 letters) compared to study eye baseline and non-study eye
- Corneal endothelial cell loss of any magnitude that necessitates corneal endothelium keratoplasty

18. STATISTICS

18.1. Statistical Methods

The primary objective of Cohort 1 was to evaluate the safety and tolerability of 4 dose levels of ENV515 (travoprost) Intracameral Implant in patients with bilateral ocular hypertension or early primary open angle glaucoma. Patients were evenly randomized (two patients per dose in the 2 ENV515-1 dose groups, 7 patients per dose in the two implants/eye ENV515-3 dose group and 11 patients per dose in the 3 implants/eye ENV515-3 dose group for a total of 20 patients) to active treatment, with one study pre-surgical eye selected to receive study medication and the other non-study eye receiving TRAVATAN Z. All arms will be enrolled in parallel.

The primary objective of Cohort 2 is to evaluate the long-term safety, and tolerability of one dose level of ENV515-3 (travoprost) Intracameral Implant. In Cohort 3 the primary objective is to evaluate the long-term safety, and tolerability of two dose levels of ENV515-3-2 (travoprost) Intracameral Implant achieved via one or two ENV515-3-2 implant(s) per eye for low and high doses of ENV515-3-2, respectively. Both Cohorts study patients with bilateral ocular hypertension or early primary open angle glaucoma. Patients will be assigned to active treatment, with one study eye selected to receive study medication and the other non-study eye receiving timolol maleate 0.5% ophthalmic solution. Study eye will be determined based on the diurnal IOP measurement at the Baseline Visit: the qualifying eye with the higher mean diurnal IOP value at the Baseline Visit will be assigned as the study eye, or the left eye will be assigned as the study eye if the mean diurnal IOP values are the same.

Assessment of safety and tolerability occurring on a weekly or monthly basis (e.g. AE reports).

Since this study has not been powered to allow formal hypothesis testing of toxicity rates or efficacy between dose groups for Cohort 1 or treatments for Cohort 2, any examination of treatment differences will be exploratory in nature. For all analyses, patient-level covariates will be summarized within each group by treatment for Cohort 1 ([Table 15](#)) or by treatment for Cohorts 2 and 3 ([Table 17](#)). Eye-level covariates will be summarized for each cell in the final row of [Table 16](#) for Cohort 1 and [Table 18](#) for Cohorts 2 and 3.

Table 15: Patient-level Analyses, Cohort 1

Group 1	Group 2	Group 3	Group 4
2 implants ENV515-3 (28.2 µg travoprost)	3 implants ENV515-3 (42.3 µg travoprost)	1 implant ENV515-1 (42.5 µg travoprost)	2 implants ENV515-1 (85.0 µg travoprost)

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Table 16: Eye-level Analyses, Cohort 1

Group 1		Group 2		Group 3		Group 4	
2 implants ENV515-3 (28.2 µg travoprost)		3 implants ENV515-3 (42.3 µg travoprost)		1 implant ENV515-1 (42.5 µg travoprost)		2 implants ENV515-1 (85.0 µg travoprost)	
ENV515-3 SE	TRAVA- TAN Z NSE	ENV515-3 SE	TRAVA- TAN Z NSE	ENV515-1 SE	TRAVA- TAN Z NSE	ENV515-1 SE	TRAVA- TAN Z NSE

SE: Study-eye; NSE: Non-study eye

Table 17: Patient-level Analyses, Cohorts 2 and 3

Cohort 2	Low Dose Cohort 3	High Dose Cohort 3
2 implants ENV515-3 (28.2 µg travoprost)	1 implant ENV515-3-2 (26.1 µg travoprost)	2 implants ENV515-3-2 (52.2 µg travoprost)

Table 18: Eye-level Analyses, Cohort 2 and 3

Cohort 2		Low Dose Cohort 3		High Dose Cohort 3	
2 implants ENV515-3 (28.2 µg travoprost)		1 implant ENV515-3-2 (26.1 µg travoprost)		2 implants ENV515-3-2 (52.2 µg travoprost)	
ENV515-3 SE	Timolol maleate 0.5% NSE	ENV515-3-2 SE	Timolol maleate 0.5% NSE	ENV515-3-2 SE	Timolol maleate 0.5% NSE

SE: Study-eye; NSE: Non-study eye

18.1.1. Patient Disposition, Demographic and Background Characteristics

Baseline demographic characteristics such as age and gender and clinical characteristics including VA, IOP, gonioscopy, and corneal thickness will be summarized using descriptive statistics. Baseline will be defined as the last measurement prior to administration of the first dose of study drug.

18.1.2. Analysis of Safety

Safety endpoints include AEs, corneal thickness, VA, endothelial cell count and morphology, slit lamp biomicroscopy exam findings, corneal staining, binocular indirect ophthalmoscopy, VF assessment, anterior segment photos, pupil measurement, vital signs, clinical laboratory values, physical exam findings, and rate of discontinuation from the study. Compliance with study drug administration will also be collected.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and categorized by system organ class using preferred terms. Events will be tabulated with respect to

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their intensity and relationship to the study drug. Changes in corneal thickness, VA, endothelial cell count and morphology, slit lamp biomicroscopy exam findings, binocular indirect ophthalmoscopy, VF assessment, anterior segment photos, and pupil measurement will be summarized and compared between treated study eyes and across study arms for Cohort 1 and between study eyes for Cohorts 2 and 3 using descriptive statistics. Continuous clinical laboratory values will be summarized using mean and standard deviation for reported and change from baseline values. Categorical clinical laboratory values will be summarized using shift tables displaying the frequencies of patients with abnormal or normal results. In addition, patient specific data listings will be provided for all safety measurements.

All SAEs and other significant events, including withdrawals due to AEs will be individually summarized in the clinical study report.

18.2. Sample Size Estimation

Since this trial is primarily a dose-finding safety and tolerability study and the first study of ENV515 in patients for Cohort 1, and the first study of the full duration of IOP-lowering effect of ENV515-3 for Cohort 2, sample size estimation was not performed. This study will enroll up to four arms of 2 to 11 patients each treated unilaterally for approximately 20 patients for Cohort 1 and 5 patients in a single arm for Cohort 2, and 15 patients in Cohort 3.

The proposed number of patients is typical for a Phase 1/2a clinical trial and should be sufficient to assess the safety and tolerability of the study drug. Assuming that 5 patients receive pooled active drug within Cohort 1, the probability of failing to observe a toxicity can be determined for various true underlying toxicity rates from the binomial distribution (Table 19). For example, for a true underlying toxicity rate of 30%, the probability of failing to observe toxicity with 5 patients would be 0.17. For a true toxicity rate of 40%, the probability of failing to observe toxicity would be 0.08. For Cohort 3, the probability of failing to observe toxicity was determined for $n=5$ and $n = 10$ patients to provide powering information for the minimum power in this cohort targeting 15 patients in low ($n \sim 5-10$) and high ($n \sim 10$) dose groups, respectively (Table 19 and Table 20).

Table 19: Toxicity Probabilities (n = 5), Cohorts 1, 2, and 3

True Toxicity Rate (%)	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Failing to Observe Toxicity	0.59	0.33	0.17	0.08	0.03	0.01	0.002	<0.001	<0.001

Table 20: Toxicity Probabilities (n = 10), Cohort 3

True Toxicity Rate (%)	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Failing to Observe Toxicity	0.35	0.11	0.03	0.006	0.001	<0.001	<0.001	<0.001	<0.001

Due to the study design and discontinuation criteria in the protocol, patients who receive the ENV515 dose of study treatment and discontinue from the study for any reason may be replaced.

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18.3. Level of Significance

All exploratory statistical tests will be 2-sided and nominal significance will be determined at the 0.05 level.

18.4. Procedure for Accounting for Missing, Unused, or Spurious Data

Any missing, unused, or spurious data will be noted in the final statistical report.

18.5. Procedure for Reporting Deviations from the Statistical Plan

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

18.6. Patients to be Included in the Analysis

AEs and other safety parameters will be analyzed for all patients receiving at least one dose of study medication in the study (Safety population).

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will permit trial-related monitoring, audits, Institutional Review Board (IRB) review, and regulatory inspection(s) by providing direct access of source data and documents (such as tests performed as a requirement for participation in the study and other medical records required to confirm information contained in the case report form such as medical history) to the appropriate authorized persons conducting such reviews.

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20. QUALITY CONTROL

The progress of the study will be monitored by on-site, written, email, and telephone communications between personnel at the study center and the sponsor (or designated monitor). The investigator will allow Envisia monitors or designee to inspect all case report forms; patient records (source documents); signed informed consent forms; records of study medication receipt, storage, and disposition, and regulatory files related to the study.

21. ETHICS

21.1. Institutional Review Board (IRB)

This protocol and the informed consent form (ICF) must be approved by the appropriate IRB and the approvals made available to Envisia or designee prior to the start of the enrollment into the study based on these items. Materials used to recruit patients will be approved by the appropriate IRB and the approvals made available to Envisia or designee prior to their use. In addition, the IB should be submitted to the IRB. Written IRB approval must adequately identify the protocol and informed consent form. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to Envisia Therapeutics Inc. (or designated monitor).

Any modification of study procedures or amendments to the protocol must be approved by the IRB prior to implementation. In the event that a modification or amendment is considered by the investigator to be immediately necessary to ensure patient safety, the investigator will promptly notify their IRB and Envisia Therapeutics Inc.

Investigators will promptly report all SAEs occurring at their site to their IRB.

21.2. Informed Consent Requirements

It is the responsibility of the investigator to obtain signed written informed consent from each potential study patient prior to the conduct of any screening or other study procedures. This written informed consent will be obtained after the methods, objectives, and potential risks of the study have been fully explained to the potential patient. The investigator must explain to each patient that he or she is completely free to refuse to enter the study or to withdraw from it at any time.

The patient should also be asked in the informed consent form for permission for the principal investigator or his/her designee to contact the patient's other personal physicians, as appropriate, concerning participation in the study.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. A properly executed written ICF shall be read, signed, and dated by each patient prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept on file at the study site. Patients will be given a copy of the signed ICF and will be informed of any new developments during the course of the study that might influence their continued participation in the study.

The investigator or a qualified designee will be available to answer each patient's questions throughout the study, and all questions must be answered to their satisfaction. If the protocol is amended and a revised ICF is introduced during the study, each patient's further consent must be obtained. The new version of the ICF must be approved by the EC/IRB prior to subsequently obtaining each patient's consent.

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Receipt of written informed consent will be documented in each patient's eCRF. The signed ICF must remain in each patient's study file and must be available for verification by study monitors at all times.

21.3. Maintaining Privacy and Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, and other documents, including communications between the study site and Envisia, will identify patients in a fully anonymized manner, for example using only their initials and/or their assigned study identification numbers. If required, the investigator will grant monitors and auditors from Envisia or its designee and/or regulatory authority's access to patients' original medical records for verification of the data gathered on the eCRFs and to audit the data collection process. Patients' confidentiality will be maintained and will not be made publicly available unless mandated by applicable laws and regulations.

22. DATA HANDLING AND RECORDKEEPING

All procedures for the handling and analysis of data will be conducted using good clinical practices meeting ICH guidelines and US Food and Drug Administration regulations for the handling and analysis of data for clinical trials.

22.1. Data Quality Control and Reporting

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the Standard Operating Procedures (SOPs) of Envisia and the contracted CRO(s). The investigator will assume the responsibility of ensuring the completeness and accuracy of the clinical data. All data will be verified for quality control and will also be subject to audits from Envisia or designee to ensure quality.

All laboratory results will be analyzed by an accredited and licensed clinical laboratory facility. Clinical laboratory data will be transferred from the central laboratory to the clinical database maintained by the CRO.

All qualified central reading centers will collect, maintain and analyze study data in accordance to their standard operation procedures. Their data will be transferred to the clinical database.

The responsible clinical study monitor(s) will check data at the monitoring visits to the clinical study site. The investigator will ensure that the data collected are accurate, complete, and legible. Any changes made to the clinical data will be documented with a full audit trail.

Aspects of the clinical and statistical phases of the study, including all associated documentation, may be reviewed by the Quality Assurance Unit of the CRO using a risk-assessment approach. The final clinical and statistical report will be audited to ensure that, as far as can be reasonably established, the methods described and the results reported accurately reflect the raw data generated during the study.

22.2. Records Retention

Study site files for the retention of regulatory documents will be established at the beginning of the study, maintained for the duration of the study, and retained according to FDA and ICH/GCP guidelines and applicable regulatory requirements. The records maintained must be adequate to fully document appropriate protection of study patients, the validity of the study, the integrity of the data, and the manner in which the study was conducted.

The investigator's site file, copies of protocols, CRFs, originals of test result reports, drug disposition logs, correspondence, records of written informed consent, and other paper or electronic documents pertaining to the conduct of the study must be kept on file by the investigator and in readily accessible order for at least 2 years after the last approval of a marketing application, until at least 2 years have elapsed after formal discontinuation of the clinical development of the investigational product, or according to local regulatory requirements. No study document may be destroyed without prior written consent from Envisia or its designee. Should the investigator wish to withdraw from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.

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Envisia must be notified in writing in advance if a custodial change is to occur. It is important that the investigator remain ready to provide background information from the archived study records on request.

The sponsor or designee will maintain adequate study records for at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. After that period, the sponsor will be contacted to determine whether the study records will be forwarded to the sponsor, destroyed, or kept at the location of the designee or another facility for a longer period of time.

23. PUBLICATION POLICY

The institutions and investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of Envisia.

24. REFERENCES

1. TRAVATAN® (travoprost ophthalmic solution) Package Insert. Alcon Laboratories, Inc. Fort Worth, TX 2004.
2. TRAVATAN Z® (travoprost ophthalmic solution) Package Insert. Alcon Laboratories, Inc. Fort Worth, TX. 2013.
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4. Quigley HA. Glaucoma Macrocosm to microcosm. *Invest Ophthalmol & Visual Sci.* 2005;46(8):2663-2670.
5. Caprioli J, Rohit V. Intraocular Pressure: Modulation as treatment for Glaucoma. *Am J Ophthalmol.* 2011;152(3):340-344.
6. OZURDEX® (dexamethasone intravitreal implant) Package Insert. Allergan, Inc. Irvine, CA 2014.
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8. Timolol Maleate Ophthalmic Solution, USP (0.5% Sterile Ophthalmic Solution) Package Insert. Akorn, Inc. Lake Forest, IL
9. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140:509-516.

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APPENDIX 1

Blood/Plasma Sample Collection and Processing, Cohorts 1, 2 and 3

Chemistry and hematology collection and processing instructions can be found in the ACM lab manual.

Plasma samples will be processed as follows:

Collect whole blood into vial K₂EDTA provided by ACM. Centrifuge for 15 minutes at 2,000 x g to deplete platelets in the plasma sample. The resulting supernatant is designated plasma. Immediately transfer the liquid component (plasma) into a plasma cryovial provided by ACM using a Pasteur pipette. The samples should be maintained at 2-8°C while handling. The plasma should be aliquoted into a primary and secondary cryovials, stored, and transported at -20°C or lower. It is important to avoid freeze-thaw cycles.

No plasma samples should be shipped on Fridays. If plasma samples are collected on a Friday, please store in a controlled -80°C to -70°C freezer if you have one. If you do not have a -80°C to -70°C freezer, please fill the shipment container to capacity with dry ice and hold shipment over the weekend. Replenish the dry ice on Monday and ship samples overnight for Tuesday delivery. *Do not put dry ice in a -20°C freezer.

Aqueous Humor Sample Collection and Processing, Cohort 1

Aqueous humor will be collected as follows:

Following the creation of the initial incision in the clear cornea, ~100 µL of aqueous humor will be sampled from the anterior chamber via provided 1 ml syringe with 30 gauge needle. Samples will be dispensed into pre-labeled amber scintillation vial. Place sample in dry ice for shipment to Intertek on the same day.

Target Volume: ~0.1 mL

Aqueous humor samples will be collected and processed.

If implants are removed from patients in Cohorts 2 or 3, utilize the collection of aqueous humor collection and processing above.

No aqueous humor samples should be shipped on Fridays. If aqueous humor samples are collected on a Friday, please store in a controlled -80°C to -70°C freezer if you have one. If you do not have a -80°C to -70°C freezer, please fill the shipment container to capacity with dry ice and hold shipment over the weekend. Replenish the dry ice on Monday and ship samples overnight for Tuesday delivery. *Do not put dry ice in a -20°C freezer.

Implant Removal and handling, Cohort 1

The recovered implants recovery is described in this study protocol. The recovered implants will be collected and handled as by the following procedure:

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After removal of the aqueous humor sample, implants will be recovered from the anterior chamber. A stream of Buffered Saline Solution (BSS) is directed to the iridocorneal angle location where the implant(s) was identified during gonioscopy. Dislodge the implants using the stream of BSS. Implants will float within the fluid on the anterior chamber. Utrata forceps or equivalent instrument is used to grasp implant(s) and remove through the incision. Place implant(s) in salinized glass vials and store at 2-8°C until shipment. Samples should be shipped the same day as recovery.

If implants are removed from patients in Cohorts 2 or 3, utilize the removal and handling proceeds above.

No recovered implants should be shipped on Fridays. If recovered implants are collected on a Friday, please store in a controlled 2°C to 8°C refrigerator.