SUMMITANALYTICAL	**CONFIDENTIAL**

Ocuphire Pharma, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title: Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Orally Administered APX3330 in Subjects with Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy or Mild Proliferative Diabetic Retinopathy

Study Number: OPI-APXDR-201 (ZETA-1)

Phase: Phase 2

Sponsor: Ocuphire Pharma, Inc.
37000 Grand River Avenue, Suite 120
Farmington Hills, MI 48335 USA

Author: [redacted]

Date: 2022-12-16

Status: FINAL V1.0

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the analysis plan are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
AE	adverse event
ARP	All Randomized Population
ATC	Anatomical Therapeutic Chemical
BCVA	best-corrected visual acuity
BP	blood pressure
CEO	Chief Executive Officer
CRF	Case Report Form
CS	clinically significant
CST	central subfield thickness
DD	drug dictionary
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Score
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
HbA1c	Hemoglobin A1c
HR	heart rate
IOP	Intraocular pressure
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-To-Treat
NCS	not clinically significant
NPDR	non-proliferative diabetic retinopathy
OD	right eye
OS	left eye
OU	both eyes
PMM	pattern mixture model
PRP	panretinal laser photocoagulation

Abbreviation/Term	Definition
PP	Per Protocol
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SOC	system organ class
SP	Safety Population
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
VA	visual acuity
VEGF	vascular endothelial growth factor
WHO	World Health Organization

3. INTRODUCTION

3.1. Preface

This document presents an analysis plan for the Ocuphire Pharma, Inc. Protocol OPI-APXDR-201 (ZETA-1) (*Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Orally Administered APX3330 in Subjects with Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy or Mild Proliferative Diabetic Retinopathy*).

Reference materials for this plan include the protocol OPI-APXDR-201 amendment 4 (27SEP2021) and Case Report Forms (CRFs) Version 4.0 (15APR2022).

3.2. Purpose of Analyses

The ZETA-1 study is a placebo-controlled, double-masked, randomized, Phase 2 study in a maximum of 100 randomized subjects with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) or mild proliferative diabetic retinopathy (PDR), evaluating safety and efficacy following oral administration of APX3330 twice daily for 24 weeks.

Ocuphire plans to [redacted]

3.3. Deviations from Study Protocol

[redacted]

4. STUDY OBJECTIVES

The objectives of this study are as follows:

Primary objective

- To evaluate the efficacy of APX3330 to improve Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Score (DRSS) in subjects with moderately severe to severe NPDR or mild PDR.

[redacted]

4.1. Study Endpoints

4.1.1. Primary Endpoints

The primary efficacy endpoint is the percent of subjects with a ≥ 2-step improvement in DRSS in the study eye at Week 24.

[redacted]

Secondary efficacy endpoints

[redacted]

[redacted]

Measurements:

[redacted]

[redacted]

Safety endpoints will include:

- Incidence and severity of systemic and ocular AEs
- Change from baseline in body system assessments
- Change from baseline in vital sign measurements
- Change from baseline in clinical laboratory assay results (blood chemistry, hematology)
- Change from baseline in intraocular pressure (IOP)
- Change from baseline in slit lamp examination parameters
- Change from baseline in dilated funduscopic examination parameters

[redacted]

5. STUDY METHODS

5.1. General Study Design and Plan

A maximum of 100 male or female subjects aged ≥ 18 years with DR rated as moderately severe to severe NPDR (DRSS Level 47 or 53) or mild PDR (DRSS Level 61) will be randomized in a 1:1 ratio to one of two treatment arms, with the expectation that approximately 96 subjects will be evaluable for efficacy. Randomization will be stratified by level of disease severity (NPDR or PDR), and subjects with mild PDR will be capped at 20% for each arm. Patients with DME in the fellow eye will be eligible for enrollment into the study, however center involved DME in the study eye is exclusionary.

The eligible eye with the highest DRSS will be designated as the study eye for the primary endpoint efficacy analysis. If the PDR cap has been reached, the study eye may be an eye with the lower DRSS if the other eye has mild PDR. If eyes have the same DRSS, the eye with the worse BCVA will be selected as the study eye. If the DRSS and BCVA are equivalent between eyes, study eye will be the right eye (OD).

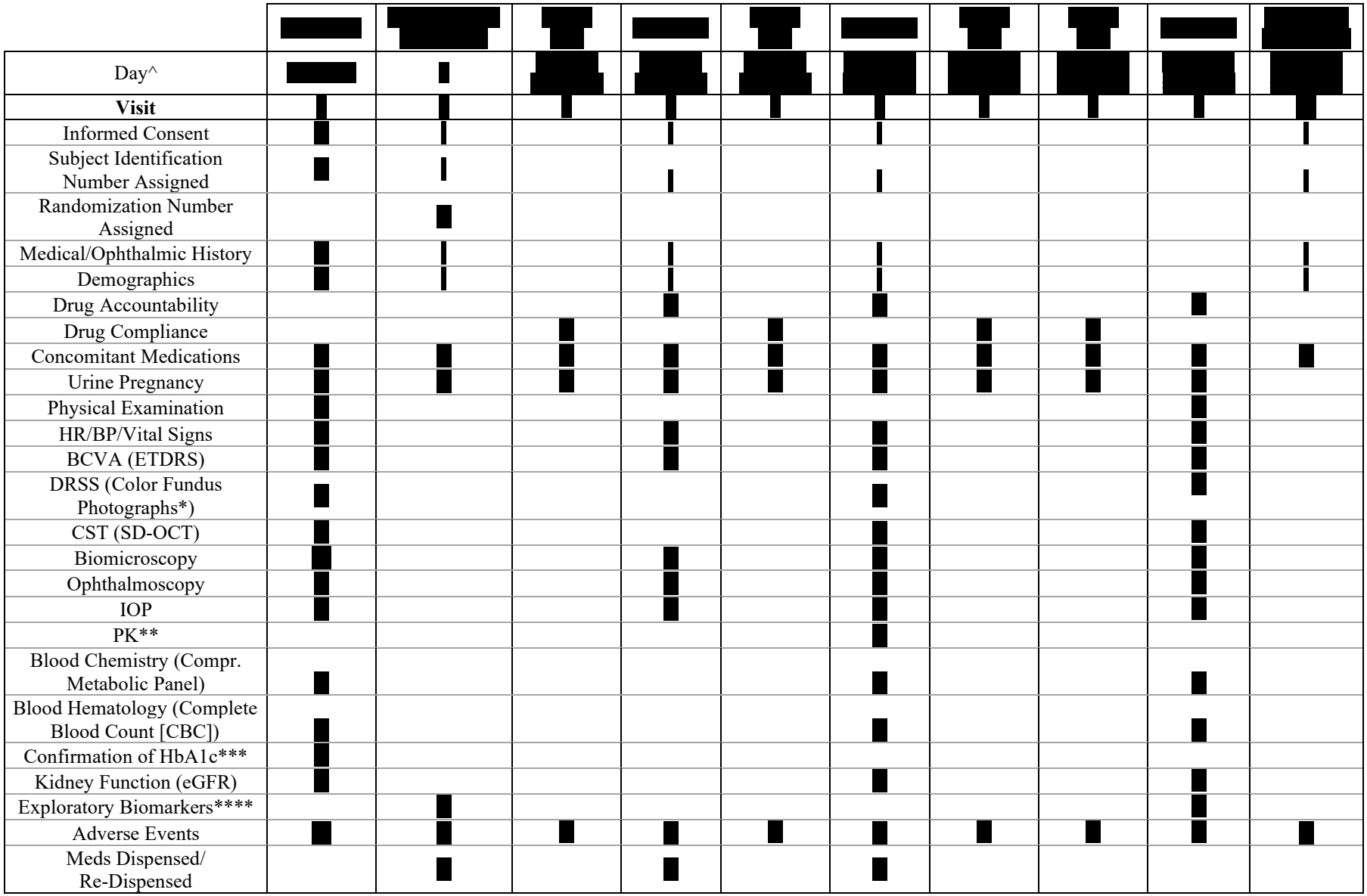
Subjects will be screened at Visit 1 and those successfully completing eligibility requirements will return to site for their Qualification/Baseline Visit (Visit 2/Day 1) where they will undergo a set of safety and lab test assessments and study medication will be dispensed. Subjects will then return to site at Visit 4 (Week 4), Visit 6 (Week 12) and Visit 9 (Week 24) for safety and efficacy assessments. In between these site visits, subjects will be contacted by telephone on Visit 3 (Week 1), Visit 5 (Week 8), Visit 7 (Week 16), and Visit 8 (Week 20) for a safety assessment to include AEs, concomitant medications, and drug accountability.

Study medication will be dispensed initially at Visit 2 (Day 1) and then at Visit 4 (Week 4) and Visit 6 (Week 12) at the site. Subjects will bring all unused study medication to each site visit for drug accountability. Study medication will be collected at site during Visit 9 (Week 24). A Follow-up Phone Call will be conducted one week after Visit 9 (Week 24) for AE and concomitant medication assessments.

Subjects will take five 120 mg tablets (APX3330 or placebo) by mouth each day, with 3 tablets every morning and 2 tablets every evening for 24 weeks. Study medication should be taken at approximately the same time each day and may be taken with or without food.

The schedule for assessments and timing of events is presented in Table 1.

Table 1 Screening, Qualification/Baseline, Treatments, and Follow-up Visits and Procedures



Day^										
Visit										
Informed Consent										
Subject Identification Number Assigned										
Randomization Number Assigned										
Medical/Ophthalmic History										
Demographics										
Drug Accountability										
Drug Compliance										
Concomitant Medications										
Urine Pregnancy										
Physical Examination										
HR/BP/Vital Signs										
BCVA (ETDRS)										
DRSS (Color Fundus Photographs*)										
CST (SD-OCT)										
Biomicroscopy										
Ophthalmoscopy										
IOP										
PK**										
Blood Chemistry (Compr. Metabolic Panel)										
Blood Hematology (Complete Blood Count [CBC])										
Confirmation of HbA1c***										
Kidney Function (eGFR)										
Exploratory Biomarkers****										
Adverse Events										
Meds Dispensed/ Re-Dispensed										

BCVA=best-corrected visual acuity; BP=blood pressure; CST=central subfield thickness; DRSS=Diabetic Retinopathy Severity Score; eGFR=estimated glomerular filtration rate; ELISA=enzyme-linked immunosorbent assay; ETDRS=Early Treatment Diabetic Retinopathy Study; HR=heart rate; IOP=intraocular pressure; PK=pharmacokinetic; SD-OCT=spectral-domain optical coherence tomography.

^ Day of study refers to number of weeks and days after date of randomization.

^^If the subject meets all the inclusion criteria and none of the exclusion criteria, this Qualification Visit becomes the Baseline Visit. A subject identification number is assigned after the subject is qualified.

*DRSS. The ETDRS classification can be found in Report Number 10 and is based on fundus photography, which includes 7 overlapping stereoscopic 30° photographic fields. 4-wide field photographs have subsequently been shown to provide equivalent results.

[redacted]

***Either by subject-provided report, primary care physician, or local or central lab test.

****Exploratory biomarkers in plasma will be examined with an ELISA (Ref-1 levels) and a cytokine panel.

5.2. Inclusion – Exclusion Criteria and General Study Population

The study population will be a maximum of 100 subjects with moderately severe to severe NPDR (DRSS Level 47 or 53) or mild PDR (DRSS Level 61), with approximately 96 evaluable subjects (i.e., who have at least one post-randomization DRSS evaluation in the study eye, who have missed less than 20% of expected doses, and do not have any major protocol deviations considered to have significant impact on treatment outcome). Written informed consent will be obtained from each subject.

The inclusion and exclusion criteria defined in the protocol apply to all subjects and are not repeated herein. Reference is made to the final protocol for the specific inclusion and exclusion criteria for study subjects.

5.3. Randomization and Blinding

At the initiation of study-related procedures (Visit 1), every subject who is screened is assigned a subject identification number in numerical order within site. Once a subject is qualified for the study (Visit 2), the subject is assigned a randomization number provided by the biostatistician in the electronic data capture (EDC) system. Randomization will be stratified by level of disease severity (NPDR or PDR) and subjects with mild PDR will be capped at 20% for each arm.

Study medication will be masked to both Investigator and study subjects, as well as Ocuphire. Assignment to treatment sequence will be masked to the Investigator, Ocuphire, and the subjects.

5.4. Analysis Variables

Variables to be summarized include:

- Subject disposition
- Demographics and baseline characteristics
- Protocol deviations
- Prior and concomitant medications
- Study medication compliance and duration of exposure
- Adverse events (AEs), Serious adverse events (SAEs), AEs leading to discontinuations, Treatment-related severe AEs, and deaths
- Body system assessment
- Ophthalmology exam findings
- Vital signs (heart rate [HR] and blood pressure [BP])
- Clinical laboratory assay results (blood chemistry, hematology)

- Best-corrected visual acuity (BCVA)
- Intraocular pressure (IOP)
- Biomicroscopy of the anterior segment including evaluation of cornea, conjunctiva, and anterior chamber; fluorescein staining will be used
- Ophthalmoscopy (dilated fundus exam including optic nerve, macula, vessels, and periphery)

6. SAMPLE SIZE

A sample size of [redacted]

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

The following analysis populations will be defined for this study.

7.1.1. Modified Intention-to-Treat (mITT)

The mITT will include all randomized subjects who received at least one dose of study treatment and had at least one DRSS efficacy measurement after study treatment. The mITT will be used for primary endpoint analysis and to analyze other efficacy endpoints, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.2. Per Protocol Population (PP)

The PP population will include all subjects in the mITT who have missed less than 20% of expected doses, who have a post-treatment DRSS measurement while on treatment or within 7 days after last dose, and do not have any major protocol deviations considered to have significant impact on treatment outcome. The PP population will be used to analyze efficacy endpoints, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.3. Completer Population

The Completer population will include all subjects in the PP population who have at least one DRSS measurement at the Week 24 visit and no rescue in the study eye. The Completer population will be to analyze efficacy endpoints, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.4. All Randomized Population (ARP)

The ARP will include all randomized subjects. This population is also known as the Intent-to-Treat (ITT) population. The ARP will be used in confirmatory efficacy analyses, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.5. Safety Population (SP)

The SP will include all randomized subjects who have received at least one dose of study treatment. The SP will be used to summarize safety variables, using the actual treatment a subject received.

7.1.6. Pharmacokinetic Population (PK)

The PK population will include all subjects in the SP who had at least one valid PK sample taken at any post-treatment timepoint. The PK population will be used to summarize PK variables, using the actual treatment a subject received.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Planned covariates include baseline values for the given assessment.

7.2.2. Planned Subgroups

Subgroup analyses by disease severity (DRSS level 47, 53, 61, and 47 or 53) will be completed for efficacy endpoints. Efficacy endpoints will also be analyzed separately for the qualified fellow eye and the non-qualified fellow eye. For the binocular DRSS secondary endpoints, a summary of fellow eyes with a baseline DRSS of 47 or higher will be completed. For the secondary endpoints of mean change from baseline in DRSS, BCVA, and CST, as well as those related to vision threatening complications, a summary of fellow eyes with baseline center-involved DME (i.e., baseline CST $\geq$ 320 μm) will be completed. Other possible subgroups include age, sex, and race.

7.3. Management of Analysis Data

7.3.1. Data Handling

Data from unscheduled visits will not be included in the analysis of efficacy or safety but will be listed.

7.3.2. Missing Data

The primary efficacy endpoint is the percentage of subjects with a $\geq$ 2-step improvement in DRSS in the study eye at Week 24. For the analysis of the primary efficacy endpoint, imputation will be performed for missing efficacy data as specified in Section 7.3.2.3 for the analysis using the mITT. Confirmatory analyses will be performed using the ARP, also using imputation for missing data.

7.3.2.1. Handling of Missing Date Values

<u>Partial or Missing Dates</u>

Missing portions of dates for AEs or concomitant medications will not be formally imputed. Instead, an AE will be classified as treatment-emergent or a medication as concomitant using the most conservative date that can be derived from the non-missing portion of the date.

7.3.2.2. Missing Baseline Data

Every effort will be made to ensure that accurate baseline information on the subjects is collected. In the event that a subject is missing baseline information, the subject will be included in the SP for assessment of safety and excluded from the primary analyses. Each case of missing baseline data will be evaluated for potential inclusion in the exploratory endpoints. All baseline data will be observed cases, without imputation.

7.3.2.3. Imputation Methods

[redacted]

[redacted]

7.3.3. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study, the early termination data will be assigned to the closest visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit, and treated as observed data for that visit in the imputation procedures described above. For subjects who had efficacy measurements taken after the last dose, all observed measurements will be used for analyses of the mITT population; for the PP Population analyses, only those measurements taken within 7 days of last dose will be treated as observed data.

7.3.4. Handling of Assessments After Rescue Treatment

In the event that an eye receives a rescue treatment, any efficacy data collected after rescue will be excluded from analysis. Rather, the data from any scheduled visits after rescue treatment will be treated as missing and will be imputed using the procedures described above.

7.3.5. Coding Conventions for Events and Medications

All AEs, medical and ophthalmic history, and concomitant procedures/therapies will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 23.1) system for reporting.

Prior and concomitant medications will be coded using WHO-DD (World Health Organization Drug Dictionary) (Version Global B3 2020-09-01).

7.3.6. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS (release 9.4 or higher) for Windows.

7.3.7. Study Data

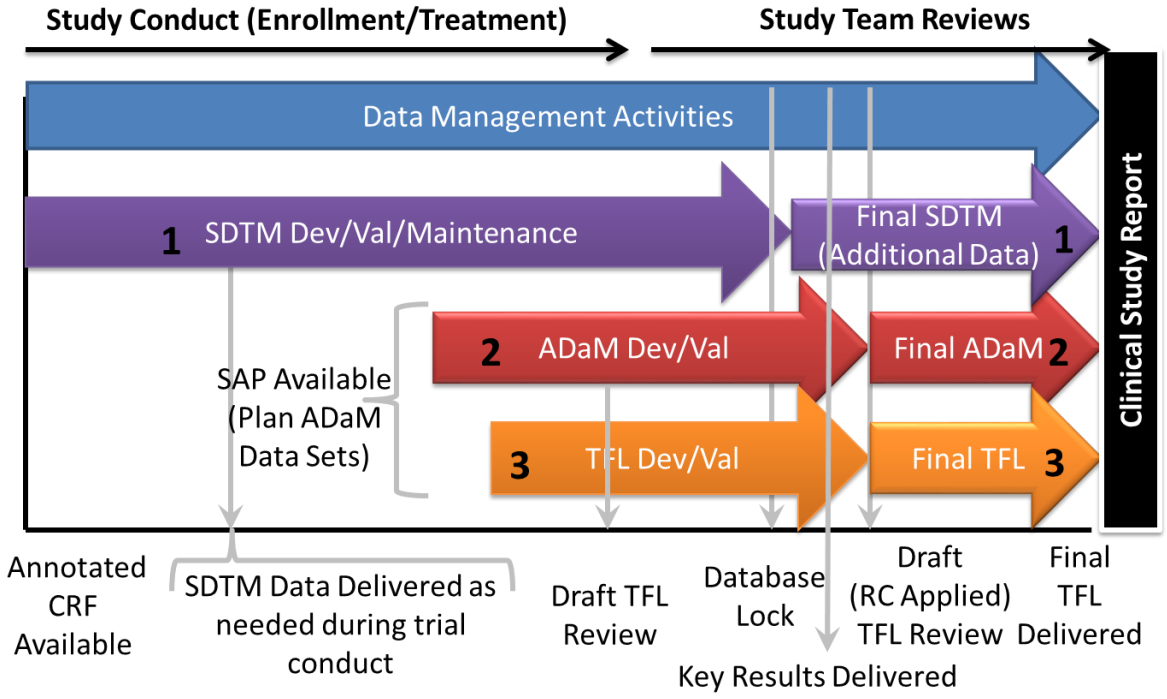
Study data identified in the schedule for time and events (Table 1) are collected, and source verified, on the EDC MedNet version 1.214.0. Clinical laboratory data (hematology, blood chemistry, and eGFR) are provided by a lab vendor (LabConnect) and provided in a spreadsheet external to the EDC. Fundus photography imaging data will be provided by the vendor Duke Reading Center; PK concentration data will be provided by the vendor AIT Bioscience; biomarker using ELISA and cytokine panel data will be provided by the laboratory of Mark Kelley at Indiana University Medical Center.

All study data will be formulated into regulatory-compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study

data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, validation, and maintenance of SDTM domains
2. Development and validation of ADaM data sets, with input source the appropriate SDTM domains.
3. Development and validation of tables, figures, and listings (TFL), with input data source the SDTM domains and analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

Categories for data presentation and analysis will consist of each treatment group (APX3330 or Placebo).

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n), mean, standard deviation, median, minimum, and maximum will be tabulated by treatment group. For categorical variables, the counts and proportions of each value will be tabulated by treatment group. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

All study-related data collected will be presented in listings. Study-related data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

7.4.2. Interim Analyses and Data Monitoring

The study will have an independent safety review committee (SRC) consisting of the Medical Monitor as well as an independent ophthalmologist. They will meet at a minimum quarterly and review all safety data and provide a written summary of safety including a specific statement regarding the safe continuation of the trial. Details are provided in the SRC Charter and SRC Analysis Plan.

7.4.3. Final Analysis and Publication of Study Results

The final analysis will be completed after all subjects have completed the study.

7.5. Multiple Testing Procedures

There will be no adjustments for multiplicity and no formal multiple testing procedures are to be implemented with this analysis plan.

7.6. Baseline Values

Baseline values are the values obtained prior to any drug administration on the evening of the Baseline Visit (Visit 2/Day 1). If the Day 1 value is missing or is not scheduled to be collected, any value collected prior to treatment administration (e.g., from the Screening visit) will be used as the baseline.

8. SUMMARY OF STUDY DATA

8.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects by treatment group and overall for the following categories: subjects in the ARP, subjects in the SP, subjects in the mITT Population, and subjects in the PP Population. All percentages will be based on the number of subjects in the ARP.

End of trial information will also be summarized in this table, including the number of subjects completing the study, the number of subjects who prematurely discontinued the study with reasons for withdrawal, the number of subjects completing the study medication dosing, and the number of subjects who prematurely discontinued the study medication with reasons for study medication discontinuation.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

8.2. Protocol Deviations

Major protocol deviations considered to have significant impact on treatment outcome will be determined by a Sponsor blinded review of the data. The Sponsor or designee will be responsible for producing the final deviation file; this file will include a description of the protocol deviation and clearly identify whether this violation warrants exclusion from the PP Population. This file will be finalized prior to database lock.

Major protocol deviations will be presented in a by-subject data listing. If the review of protocol deviations has not been completed, then all deviations will be listed.

8.3. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for the mITT, SP, PP, PK, Completer, and ARP. If any analysis populations are equivalent, then only the mITT, SP, PP, Completer, and/or PK version(s) will be generated rather than repeating equivalent summaries.

The demographics consist of age (year), sex, race, ethnicity, and study eye, and DRSS of study eye at screening (47 [Moderately severe to severe non-proliferative diabetic retinopathy], 53 [Moderately severe to severe non-proliferative diabetic retinopathy], or 61 [Mild proliferative diabetic retinopathy]). Age will be summarized using descriptive statistics. The number and percentage of subjects by sex, race, ethnicity, study eye, and DRSS of study eye at screening will also be reported. The number of and percentage of subjects whose fellow eye qualified for the study will also be reported. Percentages will be based on the total number of subjects in the study population presentation.

The following baseline characteristics will be summarized using descriptive statistics:

- DRSS (fellow eye)
- DRSS (Binocular)
- BCVA (study eye and fellow eye)
- OCT Central Subfield Thickness (study eye and fellow eye)
- IOP (study eye and fellow eye)
- Height
- Weight
- Body mass index (BMI)

8.4. Medical History

The number and percent of subjects with individual medical, ocular, and diabetic eye histories will be summarized for all subjects by treatment group and overall. Non-ocular medical history, ocular medical history, and diabetic eye history will be summarized separately.

Ocular and non-ocular medical history will be coded using the MedDRA Version 23.1. The number and percentage of subjects with any non-ocular and ocular medical history will be summarized and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of subjects in the SP. This summary will be repeated for ocular medical history occurring in the study eye, and then in the fellow eye; any ocular medical history occurring in both eyes (OU) will be counted in both the study eye and the fellow eye.

Diabetic eye history will be summarized using the questions on the CRF. The time since diagnosis of diabetic retinopathy, the time since diagnosis of center-involved DME, and the time since last anti-VEGF treatment will be calculated using the dates of each diagnosis or treatment in the CRF. Any DME, NPDR or PDR treatments associated with diabetic eye history will not be summarized but will be listed.

Subject medical history and diabetic eye history data including specific details will be presented in by-subject listings.

8.5. Prior and Concurrent Medications

The number and percentages of all concomitant medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC) level 4, and PT. The total number

of concomitant medications and the number and percentages of subjects with at least 1 concomitant medication will be summarized by treatment group. All summaries will be performed using the SP.

A concomitant medication is defined as any medication taken on or after the day of first exposure to study drug.

Prior medications are defined as any medication that has a start and stop date prior to the day of first exposure to any study drug, collected from up to 30 days prior to Screening. The total number of prior medications and the number and percentages of subjects with at least 1 prior medication will be summarized by treatment group. This summary will be repeated for ocular medications for the study eye, and then for the fellow eye; any OU medications will be counted for both the study eye and the fellow eye.

Concomitant procedures will be coded using the MedDRA Version 23.1. The number and percentage of subjects with any concomitant procedures will be summarized by treatment group for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of subjects in the SP. This summary will be repeated for ocular medical history occurring in the study eye, and then in the fellow eye; any OU ocular medical history will be counted in both the study eye and the fellow eye.

8.6. Treatment Exposure and Compliance

Exposure to study drug will be determined for each subject in the SP [redacted]

9. EFFICACY ANALYSES

Efficacy will be assessed using the mITT, PP, and Completer populations with subjects included in the treatment arm in which they were randomized.

9.1. Primary Efficacy

The primary efficacy endpoint is the difference between treatment groups in percent of subjects with a ≥ 2-step improvement from baseline in DRSS in the study eye at Week 24.

DRSS levels will be converted to steps as follows:

1 = DR severity level 10, 12 (DR absent)

2 = DR severity level 14A–14C, 14Z, 15, 20 (DR questionable, microaneurysms only)

3 = DR severity level 35A–35F (NPDR)

4 = DR severity level 43A, 43B (moderate NPDR)

5 = DR severity level 47A–47D (moderately severe NPDR)

6 = DR severity level 53A–53E (severe NPDR)

7 = DR severity level 60, 61A, 61B (PDR)

8 = DR severity level 65A–65C (moderate PDR)

9 = DR severity level 71A–71D, 75 (high-risk PDR)

10 = DR Severity 81, 85 (advanced PDR)

For the analysis of the primary efficacy endpoint, appropriate imputation techniques will be performed for missing observations or for eyes requiring rescue if applicable; details are given in Section 7.3.2.3. If the analysis using the mITT population shows a positive effect for APX-3330 at the 0.05 level of significance, the primary endpoint will be considered met. Confirmatory analyses may be performed using the ARP. Sensitivity analyses will also be performed using alternative assumptions on the missing data, with imputation performed as described in Section 7.3.2.3.

The primary efficacy endpoint will be analyzed using a logistic regression model with treatment as a factor and the baseline DRSS as a covariate. The percent of subjects in each treatment group meeting the criteria, the odds ratio (OR) with 95% confidence interval (CI), and p-value will be provided.

If there are sufficient missing data, appropriate MI methods will be applied as described in Section 7.3.2.3, and an analysis using LOCF will also be applied as a sensitivity analysis.

9.2. Secondary and Exploratory Efficacy

[redacted]

10. SAFETY ANALYSES

All safety analyses will be conducted using the SP. All safety analyses will be completed using the actual treatment a subject received. Observed case data will be used; no imputation will be performed for missing safety data except for the limited situations described in Section 7.3.2.

All safety data will be presented in by-subject listings. Unscheduled assessments will not be summarized but will be included in the listings.

10.1. Adverse Events

AEs will be coded using MedDRA, Version 23.1.

Treatment-emergent adverse events (TEAEs) are defined as any AE that begins or worsens after initiation of the investigational product and through the subject's last study visit (study completion/follow-up phone call, or early termination). Only TEAEs will be summarized in the tables and listings.

If the onset of an AE is on or after the date of first dose of study medication or is increasing in severity after first dose of study medication, then the AE will be considered treatment emergent.

The number and percent of subjects with any TEAEs will be summarized by SOC and PT by treatment group. At each level of tabulation (e.g., at the PT level), subjects will be counted only once if they had more than one such event reported during the AE collection period. This summary will be repeated for ocular TEAEs occurring in the study eye, and then in the fellow eye; any OU TEAEs will be counted in both the study eye and the fellow eye.

Note that in MedDRA, ocular events are coded to the SOC of "Eye Disorders". Thus, using SOC in the summaries will provide a separation of ocular and non-ocular adverse events.

The following summary tables will be presented for TEAE data, by SOC and PT:

- TEAEs
- Serious TEAEs
- TEAEs leading to withdrawal from the study
- TEAEs leading to study medication discontinuation
- Treatment-related severe TEAEs
- Treatment-related serious TEAEs
- Treatment-related TEAEs leading to withdrawal from the study
- Treatment-related TEAEs leading to study medication discontinuation
- TEAEs by maximum severity (mild, moderate, severe)

- Treatment-related TEAEs by maximum severity
- TEAEs by greatest relationship (not related, unlikely unrelated, possibly related, probably related, definitely related, or unknown).

Treatment-related TEAEs are defined as TEAEs with relationship to study medication possibly related, probably related, or definitely related.

All TEAEs and non-TEAEs will be presented in a by-subject listing.

10.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

10.2.1. Deaths

Fatal TEAEs, regardless of causality, will be presented in a by-subject listing.

10.2.2. Serious Adverse Events

Treatment-related treatment-emergent SAEs will be presented in a by-subject listing.

10.2.3. Adverse Events Leading to Withdrawal from the Study

Treatment-emergent AEs leading to withdrawal will be presented in a by-subject listing.

10.2.4. Adverse Events Leading to Discontinuation of Study Medication

Treatment-emergent AEs leading to discontinuation of study medication will be presented in a by-subject listing.

10.3. Vital Signs

Descriptive statistics of observed values will be presented for vital sign data at each visit (Screening, Week 4, Week 12, and Week 24), including systolic BP (mmHg), diastolic BP (mmHg), and HR (bpm) by treatment group. Changes from baseline (Screening) to each post-baseline visit will be presented.

Clinically significant vital sign measurements at any visit will be presented in by-subject listings:

- Systolic BP: > 198 mmHg
- Diastolic BP: > 121 mmHg
- HR: > 130 bpm or < 40 bpm

10.4. Physical Examination

The number and percent of subjects with normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS) physical examination results will be summarized at each visit (Screening and Week 24) by body system and treatment group.

10.5. IOP

Observed values and change from baseline (Screening) in IOP will be summarized descriptively at each visit (Screening, Week 4, Week 12, and Week 24) by treatment group. Separate summaries will be created for the study eye and the fellow eye.

10.6. BCVA

Observed values and change from baseline (Screening) in BCVA (visual acuity score using letters read as the unit) will be summarized descriptively using counts and percentages for each treatment group at each visit (Screening, Week 4, Week 12, and Week 24) by treatment group. Separate summaries will be created for the study eye and the fellow eye.

The count and percent of subjects with improvement or loss of ≥ 15, ≥ 10, and ≥ 5 letters in BCVA compared to baseline at Week 12 and Week 24 for the study eye and the fellow eye will also be summarized.

10.7. Clinical Laboratory Tests

Observed values and change from baseline in clinical laboratory results (blood chemistry, hematology, and eGFR) will be summarized descriptively for each parameter and visit (Screening, Week 12 and Week 24) by treatment group. Lab values will be summarized using standard units. Hemoglobin A1c (HbA1c) values (if available) will be included in the hematology summary.

Laboratory results flagged as “critical” by the central laboratory will be considered clinically significant and will be presented in by-subject listings.

10.8. Biomicroscopy and Ophthalmoscopy

Results from biomicroscopy and ophthalmoscopy exams will be summarized at each visit (Screening, Week 4, Week 12, and Week 24) by assessment type and treatment group.

Abnormal NCS results from biomicroscopy and ophthalmoscopy exams will be presented in by-subject listings.

10.9. Rescue Treatments

The administration of rescue treatments is recorded in the concomitant medications and the concomitant procedures/treatments CRF. The count and percent of study eyes and qualified fellow eyes requiring at least one rescue treatment will be summarized by treatment group, along with the reason(s) for rescue recorded in the CRF:

- Moderate or severe active PDR and/or development of anterior segment neovascularization
- Progression to clinically significant center involved DME

- Decrease of ≥ 10 letters in BCVA compared to baseline
- Any other finding which in the judgement of the investigator requires rescue treatment

Non-qualified fellow eyes that were treated for DME or PDR will also be summarized.

The time (in days) to first rescue treatment will be performed using a Cox proportional hazards regression model with treatment and baseline DRSS as factors. Rescues occurring prior to study drug administration will be excluded from the analysis but will be listed. Subjects who do not have rescue treatment will have their time censored at the date of last dose of study treatment. Example SAS code is as follows:

```
proc phreg data=efficacydata plots(overlay)=survival;
        class trtname;
        model timetoreturn*cnsr(1) = trtname base;
        hazardratio trtname;
        baseline covariates=efficacydata out=Pred1 survival=_all_/diradj group=trtname;
        ods output  hazardratios=hr;
run;
```

The output from the model will include the hazard ratio comparing treatment groups, its 95% CI and associated p-value. Survival plots, generated from the Cox model described above, will also be generated.

10.10. Other Safety Measures

Urine pregnancy tests for women of childbearing potential will be conducted at each study visit and presented in by-subject listings.

11. PK ANALYSES

All PK analyses will be conducted using the PK population. All PK analyses will be completed using the actual treatment a subject received. Observed case data will be used; no imputation will be performed for missing PK data.

All PK data will be presented in by-subject listings. Unscheduled assessments will not be summarized but will be included in the listings.

At the Week 12 visit, blood samples will be collected to establish drug levels from approximately 25 to 30 subjects, one sample prior to the morning dose and one sample 3 hours post–morning dose, at a subset of sites. Analysis of plasma samples for APX3330 concentration determinations will be performed by a central PK laboratory. Plasma concentrations will be summarized by time point (prior to dose and 3 hours post-dose) using descriptive statistics. For concentrations that are below the lower limit of quantification (LLOQ), the summary will use one-half the LLOQ as the analysis value.

12. REFERENCES

[1] ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline, September 1998

13. APPENDICES

13.1. List of Planned Tables

The list of planned tables includes all of the *main* tables to be presented

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