[redacted]

Confidential

Statistical Analysis Plan

Sponsor:	Opthea Limited
Protocol Title:	Phase 1b/2a study of OPT-302 in combination with aflibercept for persistent central-involved diabetic macular edema
Study Code:	OPT-302-1003
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[redacted]

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Chemical
AUC	Area Under Curve
BCVA	Best Corrected Visual Acuity
BMI	Mass Index Body
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CST	Central Subfield Thickness
CTCAE	Common Terminology Criteria for Adverse Events
DARC	Digital Angiography Reading Centre
DLT	Dose Limiting Toxicity
DME	Diabetic Macular Edema
DRSS	Diabetic Retinopathy Severity Score
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAZ	Foveal Avascular Zone
CFP	Color Fundus Photography
GLD	Greatest Linear Dimension
HbA1c	Glycated haemoglobin
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IRC	Independent Reading Centre
ITT	Intent To Treat
IVT	Intravitreal
LLT	Lowest Level Term
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRM	Model for Repeated Measures
MTD	Maximum tolerated dose

NCI	National Cancer Institute
NPDR	Non-Proliferative Diabetic Retinopathy
OCT	Optical Coherence Tomography
[redacted]	[redacted]
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
PDR	Proliferative Diabetic Retinopathy
PED	Pigment Epithelial Detachment
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SEM	Standard Error of the Mean
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

2. Introduction

This Statistical Analysis Plan (SAP) describes the proposed statistical methods to be implemented during the analysis of data collected within the scope of the Opthea Limited (Opthea) clinical study OPT-302-1003, entitled "Phase 1b/2a study of OPT-302 in combination with aflibercept for persistent central-involved diabetic macular edema (DME)". This SAP is based on the Protocol Amendment 3, dated 02 August 2018, and the study patient electronic Case Report Forms (eCRF).

All statistical considerations and analyses will be fully described in this SAP which will be finalized prior to primary database lock (and un-masking for the Phase 2a).

The ICH guideline E3 "Structure and Content of Clinical Study Reports" is used as a guide to the writing of the plan.

[redacted]

3. Study Design and Objectives

3.1 Study Objectives and Endpoints

3.1.1 Primary Objective and Endpoints

Primary objective:

- Phase 1b and Phase 2a: Evaluate the safety and tolerability of OPT-302 intravitreal (IVT) injection in combination with IVT aflibercept in participants with central-involved DME.
- Phase 2a: Assess the response rate (>=5 letter gain in Best Corrected Visual Acuity [BCVA] from baseline to week 12 according to ETDRS criteria) in participants with persistent central-involved DME receiving combination of OPT-302 and aflibercept treatment.

Primary endpoints:

- Phase 1b and Phase 2a (Safety): Subject incidence of adverse events, DLTs and clinically significant changes in vital signs, ECGs and clinical laboratory tests.
- Phase 2a (Efficacy): Response rate as defined by proportion of participants receiving combination OPT-302 and aflibercept achieving at least a 5-letter gain in BCVA compared to baseline at week 12 according to ETDRS criteria.

3.1.2 Secondary Objectives and Endpoints

The secondary objectives are to assess:

- the mean change from baseline in BCVA
- the mean change from baseline in central subfield thickness (CST) and macular volume (by spectral domain optical coherence tomography [SD-OCT])
- the percent of eyes with >=50% reduction in excess foveal thickness (SD-OCT)
- the percent of eyes with CST < 300 µm on SD-OCT
- the percent of participants with a >=2 step improvement in ETDRS Diabetic Retinopathy Severity Score

- the mean time to, and number of, retreatment injections of aflibercept anti-VEGF-A therapy during long term follow-up (week 12 to 24)
- the pharmacokinetics (PK) of OPT-302
- anti-OPT-302 antibody formation

The secondary endpoints of the study are as follows:

- Mean change in BCVA from baseline to week 12 using ETDRS criteria
- Mean change from baseline to week 12 in CST and macular volume on SD-OCT
- Percent of eyes with >= 50% reduction in excess foveal thickness from baseline to week 12 on SD-OCT
- Percent of eyes with CST < 300 µm on SD-OCT through week 12
- Percent of participants with a >= 2 step improvement from baseline to week 12 in ETDRS Diabetic Retinopathy Severity Score
- The mean time to, and number of, retreatment injections of aflibercept anti-VEGF-A therapy based on protocol specified criteria during week 12 to week 24 follow-up
- OPT-302 pharmacokinetics parameters
- Incidence of anti-OPT-302 antibody formation

3.1.3 Exploratory Objectives and Endpoints

The exploratory objectives are to evaluate:

- The CST area under the curve (AUC)
- The percent of eyes with resolution of fluid (sub-retinal fluid and intra-retinal cysts) on SD-OCT
- [redacted]

The exploratory endpoints of the study are:

- CST area under the curve (AUC)
- Percent of eyes with resolution of fluid (sub-retinal fluid and intra-retinal cysts) through week 12 on SD-OCT
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

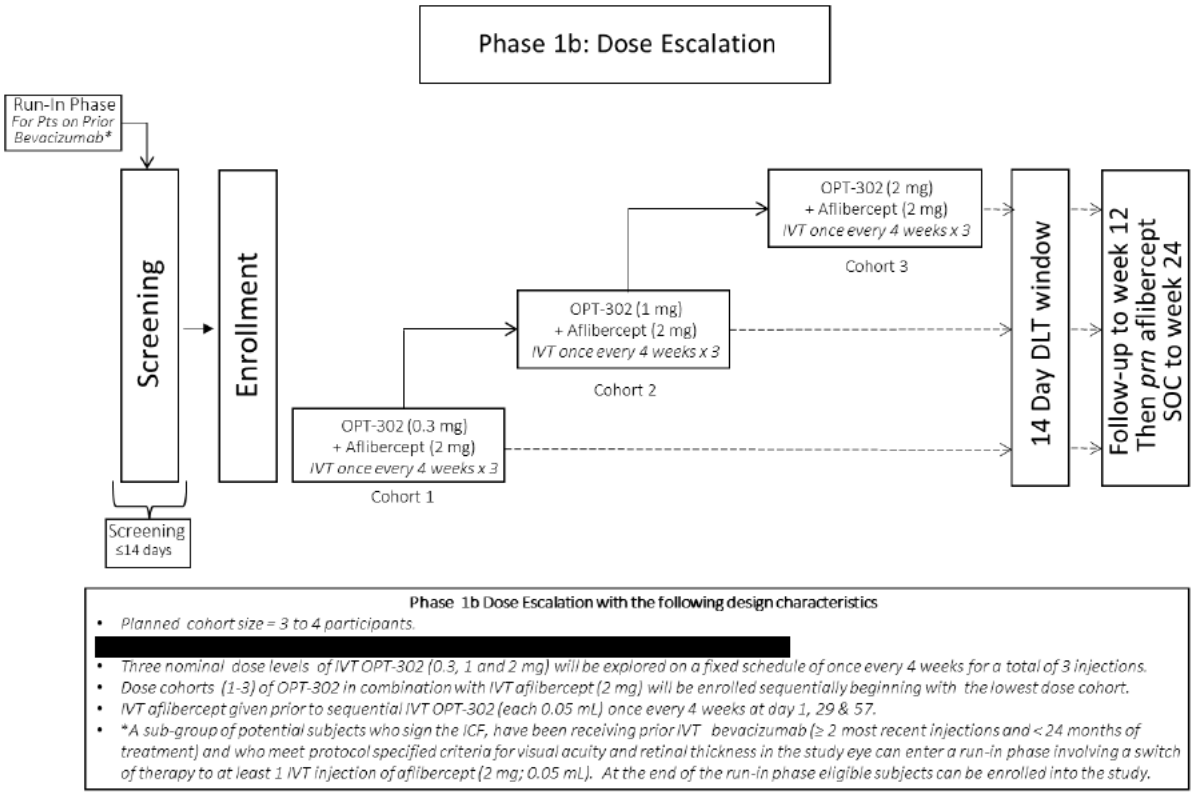
3.2 Study Design

Two part multi-center study consisting of a Phase 1b open-label, sequential dose escalation followed by a Phase 2a randomized, double-masked, dose expansion evaluating intravitreal OPT-302 in combination with aflibercept in participants with persistent central-involved DME.

The Phase 1b will consist of three sequential escalating dose levels of OPT-302 (0.3, 1.0 and 2.0 mg) used in combination with aflibercept (2.0 mg). OPT-302 and aflibercept will be administered as separate IVT injections (each 0.05mL) once every 4 weeks at Day 1, Day 29 and Day 57 with aflibercept administered first followed by OPT-302. Dose escalation will occur following the review of the cohort safety data once at least 3 patients have completed the 14 day DLT period in each dose level. [redacted]

Participants will return for a follow-up visit on Week 12 (Day 85) for assessment of vision, ocular imaging and safety assessment. A final long-term follow-up visit, at Week 24, will occur for a further assessment of vision, ocular imaging and safety assessment.

Figure 1: Study Design and Treatment Schema – Phase 1b



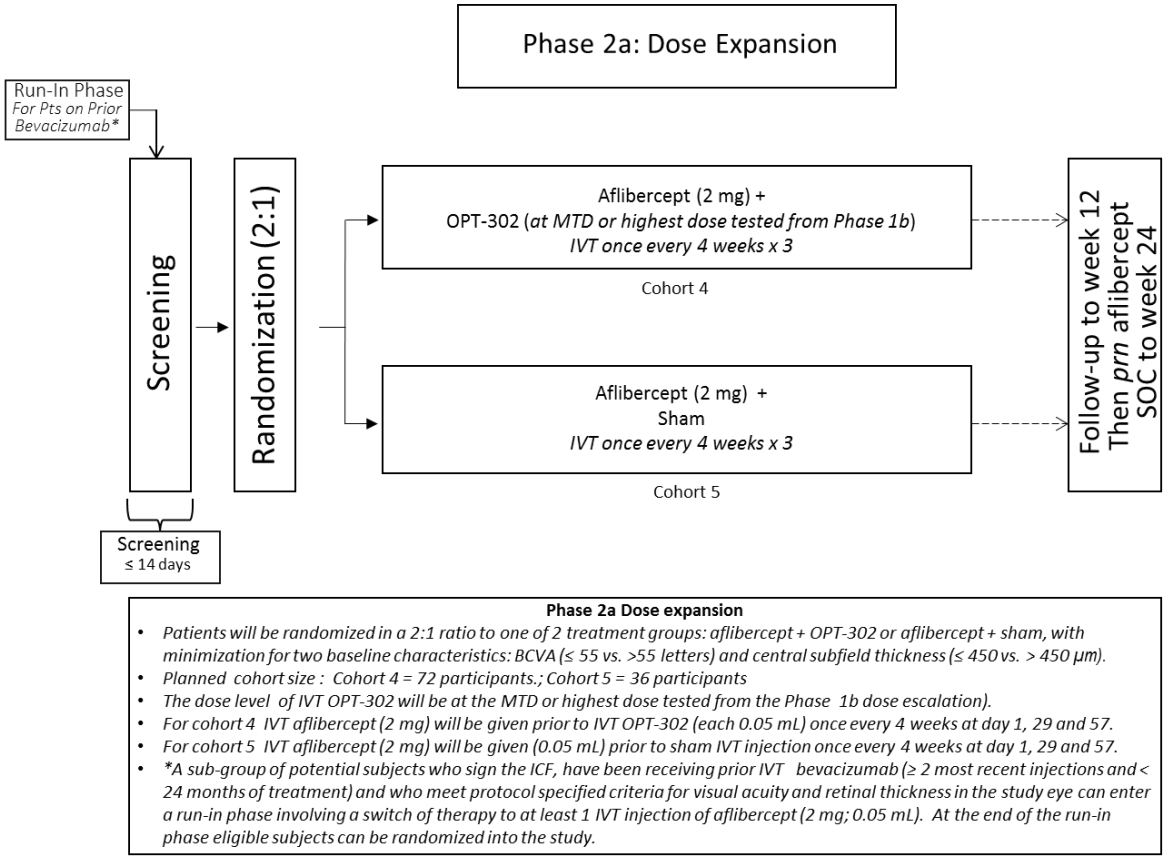
The Phase 2a randomized dose expansion will begin dependent upon agreement by the data review team based on their review of emerging safety data from the Phase 1b dose escalation phase (once all participants have completed the 14 day DLT window).

In the Phase 2a, at least 108 participants will be assigned randomly in a 2:1 ratio to one of the following two treatment groups: 2.0 mg aflibercept + OPT-302 (at MTD or highest dose tested from the Phase 1b) (Cohort 4) or aflibercept + sham (Cohort 5).

The first administration of study medication will occur once all assessments have been completed at the Baseline visit (Day 1). Participants will then attend the study site at 4-week intervals at Day 29 and Day 57, during which the participant will be assessed, and study medication will be administered.

Participants will return for a follow-up visit on Week 12 (Day 85) for assessment of vision, ocular imaging and safety assessment. A final long- term follow-up visit, at Week 24, will occur for a further assessment of vision, ocular imaging and safety assessment.

Figure 2 Study Design and Treatment Schema – Phase 2a



3.3 Dose Limiting Toxicity

A DLT is defined as any related ocular or systemic adverse event [redacted] during the first 14 days in each dose escalation cohort:

- Any adverse event >= grade 3 deemed related to the study drug(s) by the investigator
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Determination of the severity of AEs will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) v4.03. If the AE is not specified in the CTCAE, the severity will be assessed on the standard AE severity scoring system outlined in the protocol [redacted].

3.4 Randomization

In the phase 2a, participants will be randomized, using an interactive response technology [redacted] into one of two study arms by a dynamic minimisation procedure using centre, visual acuity at Baseline (<= 55 letters vs. > 55 letters), and Central Subfield Thickness (CST <= 450 vs. > 450 µm). The dynamic minimisation will use a stochastic treatment allocation algorithm, in such a way that no treatment assignment is deterministic.

3.5 Sample Size Consideration

A total of at least 81 participants receiving OPT-302 are anticipated to be enrolled in the trial (9 in Phase 1b and 72 in Phase 2a).

The table below shows the true proportion of patients with an AE that can be ruled out at various confidence levels, assuming no such event is observed in the trial.

Number of participants without adverse event	**Confidence level**		
	80%	**90%**	**95%**
3	0.48	0.57	0.63
9	0.24	0.30	0.35
81*	0.04	0.05	0.06

** If more than 72 participants are randomized to the experimental arm (aflibercept + OPT-302) in Phase 2a, the confidence levels of the total group of participants receiving OPT-302 will be higher than N=81.*

3.5.1 Phase 1b Sample Size Consideration

In the Phase 1b dose escalation, at least 9 participants are expected to be enrolled. The sample size was determined empirically and is consistent with those used in this type of initial human clinical study.

In the Phase 1b dose escalation, if 3 participants will be treated with OPT-302 per cohort (without dose limiting toxicity), a total of at least 9 participants will be treated in this phase of the trial.

3.5.2 Phase 2a Sample Size Consideration

A total of at least 108 additional participants are expected to be treated in the Phase 2a (dose expansion) study with at least 72 participants receiving OPT-302 at the MTD or the highest dose level tested from the Phase 1b, in combination with aflibercept. In case one or more of these 72 participants are not evaluable, randomization will continue and more patients will receive the same dose.

In the Phase 2a dose expansion, subjects will be allocated in a 2:1 ratio to one of two treatment groups, aflibercept with OPT-302 or aflibercept with sham, with minimization for baseline characteristics: BCVA (<= 55 vs. > 55 letters) and CST (<= 450 vs. > 450 µm). The primary outcome of the Phase 2a is the proportion of evaluable patients with a response of >= 5 letter gain in BCVA from baseline to week 12 according to ETDRS criteria in the combination aflibercept + OPT-302 group.

The design of the trial is non-comparative in so far as the sample size is calculated for the aflibercept + OPT-302 arm only. A one-stage design is used for the primary outcome (Sargent 2001) of the aflibercept + OPT-302 arm. A formal rule allows for the assessment of the observed response rate as compared with pre-specified "low" and "high" response rates. Specifically, the hypotheses of interest are H0: r <= r0 ("low" response rate) against HA: r >= r_A ("high" response rate).

The following assumptions were made for sample size calculations:

- the pre-specified "low" and "high" response rates are r_0=0.28 and r_A= 0.45
- the type I error rate (α, probability of accepting a treatment whose true response rate is lower than r_0, a false positive outcome) is set to 5%
- the type II error rate (ß, probability of rejecting a treatment whose true response rate is higher than r_A, a false negative outcome) is set to 5%
- the probability of correctly rejecting a treatment whose true response rate is lower than r_0 is set to at least 90%
- the probability of correctly accepting a treatment whose true response rate is higher than r_A is set to at least 90%

Under these assumptions, a total of 72 evaluable subjects need to be randomized to the aflibercept + OPT-302 arm. With the 2:1 randomization, a sample size of at least 108 subjects is randomized between aflibercept + OPT-302 (n=72) or aflibercept + sham (n=36). Non-evaluable participants will be replaced [redacted]. The conclusions based on the results of 72 evaluable participants in the combination aflibercept + OPT-302 arm will be:

- clinical activity if >= 27 of 72 patients have a >= 5 letter gain in BCVA from baseline to week 12 according to ETDRS criteria in the aflibercept + OPT-302 group
- insufficient clinical activity if <= 25 of 72 patients have a >= 5 letter gain in BCVA from baseline to week 12 according to ETDRS criteria in the aflibercept + OPT-302 group

[redacted]

4. General Analysis Definitions and Conventions

4.1 General Analysis Conventions

[redacted]

No tests of significance will be carried out to compare treatment arms on baseline data because any observed differences between them must be attributed to chance.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of missing values (Nmissing), number of non-missing values (n), mean, standard deviation (SD), Standard Error of the Mean (SEM), 95% confidence interval (CI), median, minimum and maximum values.

[redacted]

- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

Listings will be sorted and presented by study phase, study arm, participant, and visit day (if applicable). Listings will include both Study Eye and Fellow Eye assessments when available.

The version of the coding dictionaries like MedDRA and WHO Drug will be included in the footnotes of the applicable tables and listings.

4.2 Study Period and Visit Window Definitions

The study period for participants in the active treatment phase will be 24 weeks: 14 days for screening; 8 weeks of treatment (at Day 1 (IVT Treatment 1) , Day 29 (IVT Treatment 2) and Day 57 (IVT Treatment 3) depending on tolerability to aflibercept ± OPT-302 (or sham); and Week 12 (Follow-up) and Week 24 follow-up (Long term Follow-up) visits.

4.2.1 Schedule of Assessments

The schedule of study assessments can be found in Appendix 10.1 & 10.2 of this SAP.

4.2.2 Visit Windows

The scheduled visits, as labelled in the relevant datasets will be used in the analyses over time. No recalculation of the visits will be done. Data for the Week 12 and 24 study visits will be included in the analysis irrespective of delays to the visit outside the visit window.

Missing scheduled visit will be substituted by an unscheduled visit occurring within each visit window outlined in Appendix 10.3. [redacted]

[redacted] Data from all unscheduled visits will be included in the listings.

4.3 Planned analyses

4.3.1 Periodic Safety Review

No formal interim analysis is planned. A data review team will advise on periodic safety review of the study, as described below.

<u>Phase 1b:</u> In the open label Phase 1b, the patient safety data for each cohort will be reviewed by the data review team [redacted]. [redacted] Dose escalation will occur at the planned dose levels of OPT-302 until the MTD is determined or until the highest dose level is tested.

Phase 2a: [redacted] During the Phase 2a randomized dose expansion, there will be masked reviews of safety data by the data review team once 30, 60 and 90 participants have been randomized, received OPT-302 treatment and completed at least 14 days on study. [redacted]

4.3.2 Phase 1b Safety Analysis

A safety analysis is planned at the end of the Phase 1b. All safety endpoints will be presented on the Safety Analysis Set, and DLT data will be analyzed on the Dose Escalation Analysis Set.

4.3.3 Phase 1b/2a Primary Efficacy and Safety Analysis

The primary efficacy and safety analysis will be performed for the Phase 1b/2a when target enrollment or randomization is complete and each participant either completes the Week 12 follow-up visit or withdraws from the study prior to the Week 12 visit. This analysis will include efficacy and safety data up to and including the Week 12 visit.

4.3.4 Final Analysis

The final analysis will occur after all participants (Phase 1b and Phase 2a) complete the week 24 follow-up visit. This analysis will include efficacy and safety data up to and including week 24.

4.4 Definition of Populations

Study participants will be assigned to analysis populations as per the definitions below. All allocations will be performed prior to database lock and unmasking as part of the blinded review process. [redacted]

4.4.1 Intent-To-Treat (ITT) Analysis Set

The Intent-To-Treat (ITT) analysis set will include all participants enrolled (Phase 1b) or randomized (Phase 2a) into the study, irrespective of whether study drug(s) was administered or not. [redacted]

These analysis sets will be used to report participant disposition and to provide a sensitivity analysis of the safety and efficacy endpoints only.

4.4.2 Safety Analysis Set

The safety analysis set will comprise all participants in the ITT analysis set, but exclude those who did not receive at least one dose of study drug(s) (aflibercept or OPT-302). Participants will be analyzed according to the treatment that they actually received.

These analysis sets will be employed to determine the safety endpoints.

4.4.3 Dose Escalation Analysis Set

The analysis of dose limiting toxicity (DLT) will be conducted on the Phase 1b dose escalation analysis set defined as all DLT evaluable participants.

A participant is classified as DLT-evaluable if they have had the opportunity to complete the DLT interval (Days 1 to 14) and received at least 1 dose of OPT-302 or experienced a DLT at

any time during the first 14 days on study. [redacted]

4.4.4 Per-Protocol Analysis Set

The Per-Protocol (PP) analysis set will comprise participants in the safety dataset who were compliant with study medication, and who are considered sufficiently compliant with the protocol. The participants pertaining to the PP datasets are considered 'evaluable' participants (see more details in Section 4.7.1).

The PP analysis sets are intended to represent the subset of participants who were in the intended study population, received the intended study medication (a total of 3 scheduled IVT injections once every~ 4 weeks), and could be evaluated for study outcomes.

Efficacy analyses performed using the PP datasets will be considered as primary analysis. The primary efficacy outcome (response rate) will be analyzed using the first 72 participants randomized into the aflibercept + OPT-302 arm, available in the PP dataset, as per protocol.

[redacted]

4.6 Treatment Arms

4.6.1 Phase 1b – Dose escalation

The dose regimens for the 3 treatment cohorts in the Phase 1b are as follows:

- Cohort 1: 2 mg aflibercept and 0.3 mg OPT-302
- Cohort 2: 2 mg aflibercept and 1 mg OPT-302
- Cohort 3: 2 mg aflibercept and 2 mg OPT-302

There will be no intra-subject dose escalation in this study. Phase 1b cohorts will enroll sequentially, starting with cohort 1.

4.6.2 Phase 2a – Dose expansion

A sample size of at least 108 patients will be randomized in a 2:1 ratio between one of the following two groups:

- Cohort 4: 2 mg aflibercept + OPT-302 (at MTD or highest dose from Phase 1b)
- Cohort 5: 2 mg aflibercept + sham

4.7 Study-specific Definitions and Calculated Variables

4.7.1 Evaluable Participants

An Evaluable participant is a participant in the Phase 2a, who was randomised, received the intended study medication (a total of 3 scheduled IVT injections once every ~4 weeks), and could be evaluated for study outcomes. Evaluable patients will be used in the Per Protocol Analysis set.

[redacted]

[redacted]

4.7.2 Non-Evaluable Participants

Participants who do not meet the Evaluable participant criteria will be considered 'Non-Evaluable' and excluded from the PP analysis set. Non-Evaluable patients will be available for inclusion in the ITT and safety population sets.

4.7.3 Other Study Specific Definitions

- **Run-in Phase:** is the period 4 to 6 week prior to the Day 1 (Baseline) visit where a subset of patients who previously received bevacizumab enter the study and receive one injection of aflibercept in order to be assessed for eligibility into the study.
- **Baseline**: unless otherwise specified, baseline is defined as study Day 1, the date of the first OPT-302/Sham injection the participant received (first administration of the investigational product).
- **Baseline value**: the last value measured before first administration of investigational product. For variables/assessments not scheduled to be performed on study Day 1 or that are missing at baseline, the baseline value is the value from the screening period measured closest to study Day 1. This may include unscheduled visits done before study Day 1.
- **Study Day 1**: Study Day 1 is the day on which study medication(s) is/are first administered. [redacted]
- **Ocular AE**: An ocular AE is an AE affecting the ocular region, including the surrounding tissues. A final list of all ocular AEs reported during the study will be reviewed and agreed during masked review in conjunction with the Medical Expert and Medical Monitor.
- **Non-Ocular AE**: Non-ocular AEs are all reported AEs, excluding those that fulfil the definition of an ocular AE as above. A final list of all non-ocular AEs that occurred during the study will be reviewed and agreed during masked review in conjunction with the Medical Expert and Medical Monitor.
- **Treatment Phase**: is the 12-week period from Day 1 through to the Week 12 Follow-up Visit.
- **Week 12 Completion:** In the context of efficacy data analysis, a participant is considered to have completed the study if they have attended the Day 85 (Week 12) visit.
- **Long term Follow-up**: is the 12-week period from completion of the Week 12 Follow-up Visit through to the Week 24 Long term Follow-up visit.
- **Long term follow-up Completion**: In the context of data analysis, a participant is considered to have completed the long-term follow-up phase if they have attended Visit 11 (Week 24).

4.7.4 Other Calculated Variables

- Study Day = date of assessment – Study Day 1 +1.

[redacted]

- Duration of an adverse event (AE) (days) = date of AE resolution – date of AE onset +1. The duration will not be calculated in case of missing or incomplete dates.
- Change from Baseline (continuous data) = value at a certain visit – the Baseline value.

[redacted]

- Participants with >=2 step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Score will be determined by a change in >= 2 levels in severity (improvement) based on the table below:

Diabetic Retinopathy Severity Scale Score	Level
None	10
Mild NPDR	20
Mild-Moderate NPDR	35
Moderate NPDR	43
Moderately severe NPDR	47
Severe NPDR	53
Mild PDR	61
Moderate PDR	65
High-risk PDR	71
Advanced PDR	75
Cannot grade	90

- Duration of exposure (days) = last injection date – first injection date + 28.

[redacted]

- Treatment compliance (%) = number of injections actually received/number of injections planned*100%.

[redacted]

[redacted]

[redacted]

4.8 Data Handling Conventions

4.8.1 Handling of Missing or Partially Missing Dates

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for AEs and medications will be made to allow inclusion of appropriate data records in the analyses.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

If an AE onset date is missing or partially missing, such that it cannot be determined whether the AE started prior to the first study treatment or after the first study treatment, the AE will be classified as a Treatment Emergent AE (TEAE) i.e. an AE that started after the start of study treatment.

If time to events, or durations need to be calculated, then partially missing dates will be imputed as follows, for example, the date of diabetes diagnosis:

1) If the diagnosis date is year and month only, the day will be set to 15, provided the resulting date is not later than the start date of study treatment.
2) If the diagnosis date is year only, the month will be set to 6, and the day to 30, provided the resulting date is not later than the start date of study treatment.

4.8.2 Handling of Missing Efficacy Data

For all efficacy analyses, no missing values will be imputed. The primary efficacy analysis is based on the PP population with no missing data.

For the relevant secondary efficacy analyses, the model for repeated measures to be used considers the presence of missing data and yields valid estimates under the assumption of data missing at random, whereas-observed data will be used with no imputation (see Section 8.2.1).

4.8.3 Handling of Imaging Data

Ophthalmic imaging will be reviewed by an Independent Reading Centre (IRC) [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

All readers' recorded values will be provided in the data listings. Missing imaging data will not be imputed in any analyses.

4.8.4 Handling of Missing Data in Descriptive Analyses

When summarising categorical variables, participants with missing data are generally not included in calculations of percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of participants with missing data is presented.

When summarising continuous variables, participants with missing data are not included in calculations. When needed, the category of "Missing" is created and the number of participants with missing data will be presented. No imputations will be made.

4.8.5 Data Coding

The reported terms in medical history, ophthalmic history, medical procedures/surgeries, and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [redacted] at the Low Level Term (LLT) level per the Medical Terms Coding Conventions.

The reported terms in prior medications and concomitant medications will be coded using the WHO Drug dictionary [redacted] at the ATC Preferred Term level (the 4th level).

[redacted]

[redacted]

5. Study Participants

5.1 Disposition of Participants

The number of participants in each population (ITT, Safety, Dose Escalation and PP) and participants entered the Run-In phase, as well as the frequency of participants who discontinued the study treatment and of participants who ended the study will be given for the ITT population. The primary reason for discontinuation of the study treatment and non-completion of the study will be summarized.

All disposition data including details of the 'other reason' will be included in the listing, together with the Randomization information.

Randomization data including stratification factors will be summarized on the ITT population (Phase 2b part only).

[redacted]

5.2 Protocol Deviations

Protocol deviations will be listed for the ITT population.

All protocol deviations will be assessed and identified by the Sponsor, and will be determined as major, or not, in a masked fashion during the Masked Data Review Meeting, just prior to the primary database lock. A major protocol deviation is defined as a significant deviation from the protocol that could affect the wellbeing of the participant and/or significantly alter the endpoints of the study. The list of major protocol violations (masked and unmasked) will be provided prior to the database lock.

[redacted] The major protocol deviations will be summarized for ITT population. [redacted]

The frequency of participants excluded from the PP population will be summarized, together with the reasons for exclusion.

[redacted]

6. Demographic and other Baseline Characteristics

Descriptive statistics with respect to participant characteristics at baseline will be displayed using descriptive statistics and listed for the PP and ITT population. Baseline value has been defined in Section 4.7.3.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

Prior ocular history and medical (non-ocular) history will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for Study Eye and Non-Study Eye. Multiple occurrences of the same preferred term in one participant will be counted only once. Summary tables will be sorted alphabetically by SOC and then by PT will be sorted by decreasing frequency.

7. Prior and Concomitant Therapies

Prior and concomitant therapies will be summarized and listed on the ITT population.

7.1 Prior DME Therapies

Prior DME therapies, i.e. Anti-VEGF-A therapies, will be summarized for Study Eye and Non-Study Eye separately for the ITT and PP populations. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

All information will be detailed in a listing.

7.2 Prior and Concomitant Medications

Prior medications are defined as all medications administered prior to the first intravitreal injection of study drug(s).

Concomitant Medications are defined as all medications taken after first study injection or later until week 24.

Medications started before the first day of study treatment and continuing afterwards will be reported both as prior and concomitant.

[redacted]

7.3 Prior and Concurrent Surgeries and Procedures

Prior surgeries/procedures are defined as all surgeries/procedures performed before the first study injection. Concurrent surgeries/procedures are defined as all surgeries/procedures performed on the first study injection day or later until week 24.

Data will be separated in to ocular surgeries and procedures, and non-ocular surgeries and procedures, and summarized by MedDRA body system and preferred term, with number and percentage for both, including number and percentage of all participants with at least one surgery/procedure.

8. Efficacy Evaluation

All efficacy data will be summarized for both Phase 1b and Phase 2a. However, efficacy evaluation, i.e. treatment comparisons, will be performed based on Phase 2a data only.

The primary efficacy analysis and secondary efficacy analyses will be conducted for the PP and the ITT populations. Other exploratory/additional analyses will be conducted only for the PP analysis set.

8.1 Primary Efficacy Analysis (Phase 2a only)

The primary efficacy endpoint of the Phase 2a is the proportion of evaluable participants (i.e. in the PP set) with a response of >=5 letters gain in BCVA from baseline to week 12 according to ETDRS criteria in the combination aflibercept + OPT-302 group. The first 72 randomised evaluable participants in the aflibercept + OPT-302 group will be assessed for the primary efficacy endpoint (response rate). In addition, the response rate will also be assessed in all evaluable participants in the combination aflibercept + OPT-302 group, for all efficacy endpoints.

A summary table will present descriptive statistics by study arm of the BCVA score at baseline, the BCVA score at week 12 and the change in BCVA from baseline to week 12.

[redacted]

8.2 Secondary Efficacy Analyses

8.2.1 Mean change in BCVA from baseline to week 12

The difference in the mean change in BCVA from baseline to week 12 between treatment arms (Phase 2a only) will be tested.

A model for repeated measures, fitted by restricted maximum likelihood method, will be used for the analysis. The model will include baseline BCVA and baseline CST (as used in the randomization) as covariates. In addition, fixed effects will include treatment, visit, treatment by visit interaction, and baseline value of the corresponding endpoint (respectively BCVA, CST or macular volume) by visit interaction.

[redacted]

BCVA will also be summarized descriptively at each visit presenting actual values and changes from baseline. In addition, actual values will also be plotted by treatment arm. Listings will include data from both Study Eye and Non-Study Eye.

8.2.2 Mean change in CST (SD-OCT) from baseline to week 12

CST at each visit and change from baseline will be summarized descriptively by treatment arm. Difference in mean change in CST at week 12 from baseline between treatment arms will be analyzed using the same MRM analysis as specified in section 8.2.1 for ETDRS BCVA.

[redacted]

8.2.3 Mean change in macular volume (SD-OCT) from baseline to week 12

Macular volume at each visit and change from baseline will be summarized descriptively by treatment arm. Difference in mean change in macular volume at week 12 from baseline between treatment arms will be analyzed using the same MRM analysis as specified in section

8.2.1 for ETDRS BCVA. [redacted]

8.2.4 Change and Percent of eyes with >= 50% reduction in excess foveal thickness (SD-OCT) from baseline to week 12

[redacted] The percent of eyes with >= 50% reduction in excess foveal thickness from baseline to week 12 will be analyzed using Cochran-Mantel-Haenszel (CMH) test, adjusted for the stratification factors, i.e. baseline BCVA and baseline CST [redacted] Difference in mean change in excess foveal thickness at week 12 from baseline between treatment arms will be analyzed using the same MRM analysis as specified in section 8.2.1 for ETDRS BCVA. [redacted]

8.2.5 Percent of eyes with CST < 300 µm on SD-OCT through week 12

The percent of eyes with CST < 300 µm on SD-OCT through week 12 will be summarized by treatment arm. Treatment comparison (cohort 4 vs. cohort 5) will be performed by using CMH test adjusted for the stratification factors, i.e. baseline BCVA and baseline CST [redacted]

8.2.6 The percent of participants with a >= 2 step improvement from baseline to week 12 in ETDRS Diabetic Retinopathy Severity Score

ETDRS Diabetic Retinopathy Severity Score will be summarized at baseline and week 12. The percent of participants with a >= 2 step improvement from baseline to week 12 will be analyzed by using CMH test adjusted for the stratification factors, i.e. baseline BCVA and baseline CST [redacted]

8.2.7 Retreatment injections

The number of patients with at least one retreatment injection of aflibercept anti-VEGF-A therapy in the study eye, reason for retreatment, the mean time in days (from last study injection at Day 57) to the first retreatment injection, and the total number of retreatment injections of aflibercept anti-VEGF-A therapy based on protocol specified criteria/investigator discretion during week 12 to week 24 follow-up will be summarized and the 95% confidence intervals will be provided by treatment arm. [redacted]

Patients with bilateral DME, if they received prior bilateral Anti-VEGF-A therapy, and if they received [redacted] anti-VEGF injection between Day 1 and Day 85 in the non-study eye will be summarized separately.

Re-treatment information will also be listed.

8.3 Exploratory Efficacy Analyses

[redacted]

8.3.1 CST area under the curve (AUC)

The area under the curve of CST (observed and change from Baseline) over time will be summarized using descriptive statistics. [redacted]

8.3.2 Percent of eyes with resolution of fluid (sub-retinal fluid and intra-retinal cysts) at week 12 on SD-OCT

Number of patients with resolution of fluid at week 12 will be summarized descriptively. A patient will be considered with a resolution of fluid if sub-retinal fluid and/or intra-retinal cysts were reported at baseline ("Present" for either parameter) but not anymore at week 12 ("Absent" for both parameters). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

9. Safety Evaluation

All safety summaries will be presented using the Safety analysis set.

The analyses will be conducted according to the treatment that they received. Missing values of safety data will not be imputed; and safety summaries will be based on the observed cases.

9.1 Extent of Exposure

The extent of exposure to study medications (OPT-302/sham and aflibercept separately) will be quantified using total dose (mg), number of injections/doses, and duration of exposure (days). Total dose and duration of exposure will be summarized using descriptive statistics; (mean, median, standard deviation, standard error of the mean, minimum and maximum). Number of doses will be presented by counts and percentages.

Percent compliance and the number of missed doses will be summarized using descriptive statistics. [redacted]

[redacted]

[redacted]

9.2 Dose Limiting Toxicities

For the MTD determination, the number of participants with a dose limiting toxicity DLT (if any) will be tabulated in the Dose Escalation Analysis Set for the Phase 1b only.

DLT events for Phase 1a will be detailed in the listing.

9.3 Adverse Events

The safety analyses on AEs will be primarily based on the Treatment-Emergent Adverse Events (TEAEs) in the Treatment Phase, which is defined as an AE that was not present prior to treatment with the study product(s), or an event that was present prior to treatment, but worsens either in intensity or frequency following treatment, i.e. an AE occurring after the first administration of study medication(s) on Day 1, up to and including 28 days after the last dose of study drug, or until the Week 12, whichever comes later. [redacted]

All AEs/SAEs designated by the investigator as definitely, probably or possibly related to study medication are deemed "related" for the purposes of analysis.

An overview of TEAEs will be provided which displays the overall summary of TEAEs. Tabular summaries of the following TEAEs will be provided by SOC and PT:

- All TEAEs regardless of the relationship to study treatment
- TEAEs related to study medication
- TEAEs related to injection procedure
- TEAEs by the maximum severity grade
- All Ocular TEAEs by Study Eye and Non-Study Eye
- Ocular TEAEs (in Study Eye) related to study medication
- Ocular TEAEs (in Study Eye) related to injection procedure
- Ocular TEAEs (in Study Eye) by the maximum severity grade
- Severe TEAEs
- Severe Ocular TEAEs (Study Eye)
- TEAEs leading to Study Treatment Discontinuation
- TEAEs leading to death

Ocular AE has been defined in Section 4.6.1. More specifically, Ocular AEs are AEs with either Primary or Secondary SOC = Eye disorders or reported in the eye (OD, OS, OU).

Participants will only be counted once for each preferred term. In case the participant experienced the same adverse event more than once (based on preferred term), the worst toxicity grade will be taken.

[redacted]

All AEs, including non-TEAEs, will be detailed in participant data listings. [redacted]

The same listings will be provided separately for severe AEs, AEs leading to Study Treatment Discontinuation or Study Discontinuation, and for AEs leading to death.

9.4 Deaths and Serious Adverse Events

Serious adverse events (SAEs), ocular SAEs, non-ocular SAEs, and SAEs related to study medications/injection procedure will be summarized by system organ class and preferred term, irrespectively of the fact that they are treatment-emergent or not.

[redacted]

The number of deaths will be tabulated together with the primary cause of death. The details of the 'other cause' will be included in the listing.

[redacted]

9.6 Clinical Laboratory Determination

All laboratory data will be listed and values falling outside normal ranges will be identified, whether they will be deemed clinically relevant or not.

For the following parameters:

- **Haematology:** Red blood cells (RBC); haemoglobin; haematocrit; mean corpuscular volume (MCV); mean corpuscular haemoglobin (MCH); platelets; white blood cells (WBC) with differential (absolute count or percentage of: neutrophils, eosinophils, basophils, lymphocytes and monocytes).

- **Biochemistry:** Sodium; potassium; chloride; bicarbonate; albumin; calcium; magnesium; phosphorous; glucose; blood urea nitrogen (BUN); creatinine; creatinine kinase; total bilirubin; AST; ALT; alkaline phosphatase.
- **HbA1c**

Continuous laboratory data will be summarized using descriptive statistics for the baseline results, actual values and changes from baseline over time until week 24. The incidence of participants (number and percentage) with clinically significant abnormality identified by the investigator at any time will be evaluated by treatment arm.

[redacted]

9.7 Vital Signs and ECG

Vital signs will be summarized using descriptive statistics for the baseline results, actual values and changes from baseline over time until week 24 for the safety population. [redacted]

ECG results (Heart rate, PR, RR, QRS, QT, QTcF) will be summarized for the baseline results, actual values and changes from baseline over time using descriptive statistics. ECG interpretation/clinical significance will be summarized by means of counts and frequencies for the baseline visit and over time.

All vital signs and ECG results will also be listed.

9.8 Ophthalmic Examination and Tonometry

9.8.1 Slit Lamp Biomicroscopy

The results (normal/abnormal[redacted]) of [redacted] ophthalmic variables will be summarized at any time by treatment arm, and data at each visit will be listed in a participant data listing[redacted]

[redacted]

9.8.2 Intraocular Pressure (IOP)

IOP will be summarized by visit, including all "Pre-injection", "IOP after first injection" and "IOP after second injection" measurements, 2 hours post. Changes of IOP between any post-injections and pre-injection, and changes between pre-injection and Baseline assessment will be analyzed as continuous variables.

[redacted]

10. Appendices

10.1 Schedule of Assessments – Phase 1b

Study Procedures	Run-In Phase*	Screen Visit(s)	IVT Treatment 1						IVT Treatment 2			IVT Treatment 3				Follow-up[14]	Long term follow-up[14]
Week (*beginning*)			1				2	3	5			9				12	24
Day	≤ -42 to -21	≤ -14	1		2	4	8	15	29			57			58	85	168
[redacted]																	
Informed Consent	X*	X															
Demographics	X*	X															
Run-In Eligibility	X*																
Inclusion / exclusion criteria	X*	X	X														
Medical / Ocular / Surgical History	X*	X															
Physical Exam[1]		X															
Safety Assessments																	
Vital signs[2]		X	X		X			X	X		X	X		X		X	
ECG		X							X			X				X	
Eye Examination[3]		X	X		X			X	X		X	X		X		X	X
BCVA by ETDRS[4]		X	X					X	X			X				X	X
Concomitant Medications[5]			*Continuous assessment (through week 24)*														
Adverse Events			*Continuous assessment (through week 24)*														
Laboratory Assessments																	
Safety labs[6]		X	X						X			X				X	
HbA1c		X														X	
Urinalysis		X							X			X				X	
Pregnancy Test (urine)[7]		X	X						X			X				X	
Anti-OPT-302 antibody samples[8]	[redacted]																
PK Samples																	
Imaging																	
SD-OCT[9]		X						X	X			X				X	X
Fluorescein angiography[10]		X														X	X
Color Fundus Photography[10]		X														X	X
[redacted]																	
Study Drug IVT Admin																	
Aflibercept 2 mg	X[c]			X						X			X			13X[pm]	
OPT-302[12]				X						X			X				

ADA = Anti-Drug Antibody for OPT-302; BCVA = Best Corrected Visual Acuity; DLT = Dose Limiting Toxicity; ETDRS = Early Treatment of Diabetic Retinopathy Study; FA = Fluorescein Angiography; PK = Pharmacokinetic; SD-OCT = Spectral Domain Optical Coherence Tomography

[redacted]

10.2 Schedule of Assessments – Phase 2a

Study Procedures	Run-In Phase*	Screen Visit(s)	IVT Treatment 1			IVT Treatment 2			IVT Treatment 3			Follow-up[16]	Long term follow-up[16]
Week (*beginning*)			1			5			9			12	24
Day	≤ -42 to -21	≤ -14	1			29			57			85	168
[redacted]													
Informed Consent	X*	X											
Demographics	X*	X											
Run-In Eligibility*	X[c]												
Inclusion / exclusion criteria	X[c]	X	X										
Medical / Ocular / Surgical History	X*	X											
Physical Exam[1]		X											
Safety Assessments													
Vital signs[2]		X	X		X	X		X	X		X	X	
ECG		X				X			X			X	
Eye Examination[3]		X	X		X	X		X	X		X	X	X
BCVA by ETDRS[4]		X	X			X			X			X	X
Concomitant Medications[5]			*Continuous assessment (through week 24)*										
Adverse Events			*Continuous assessment (through week 24)*										
Laboratory Assessments													
Safety labs[6]		X	X			X			X			X	
HbA1c		X										X	
Urinalysis		X				X			X			X	
Pregnancy Test (Urine)[7]		X	X			X			X			X	
Anti-OPT-302 antibody samples[8]	[redacted]												
[redacted]													
Imaging													
SD-OCT[10]		X				X			X			X	X
Fluorescein angiography		X										X	X
Color Fundus Photography[11]		X										X	X
OCT-A (*sub-study*)[12]		X				X			X			X	
Study Drug IVT Admin & Randomization													
Interactive Randomization system, IXRS[13]		X	X										
Aflibercept 2 mg	X[c]			X			X			X		[15]X[am]	
OPT-302 or Sham[14]				X			X			X			

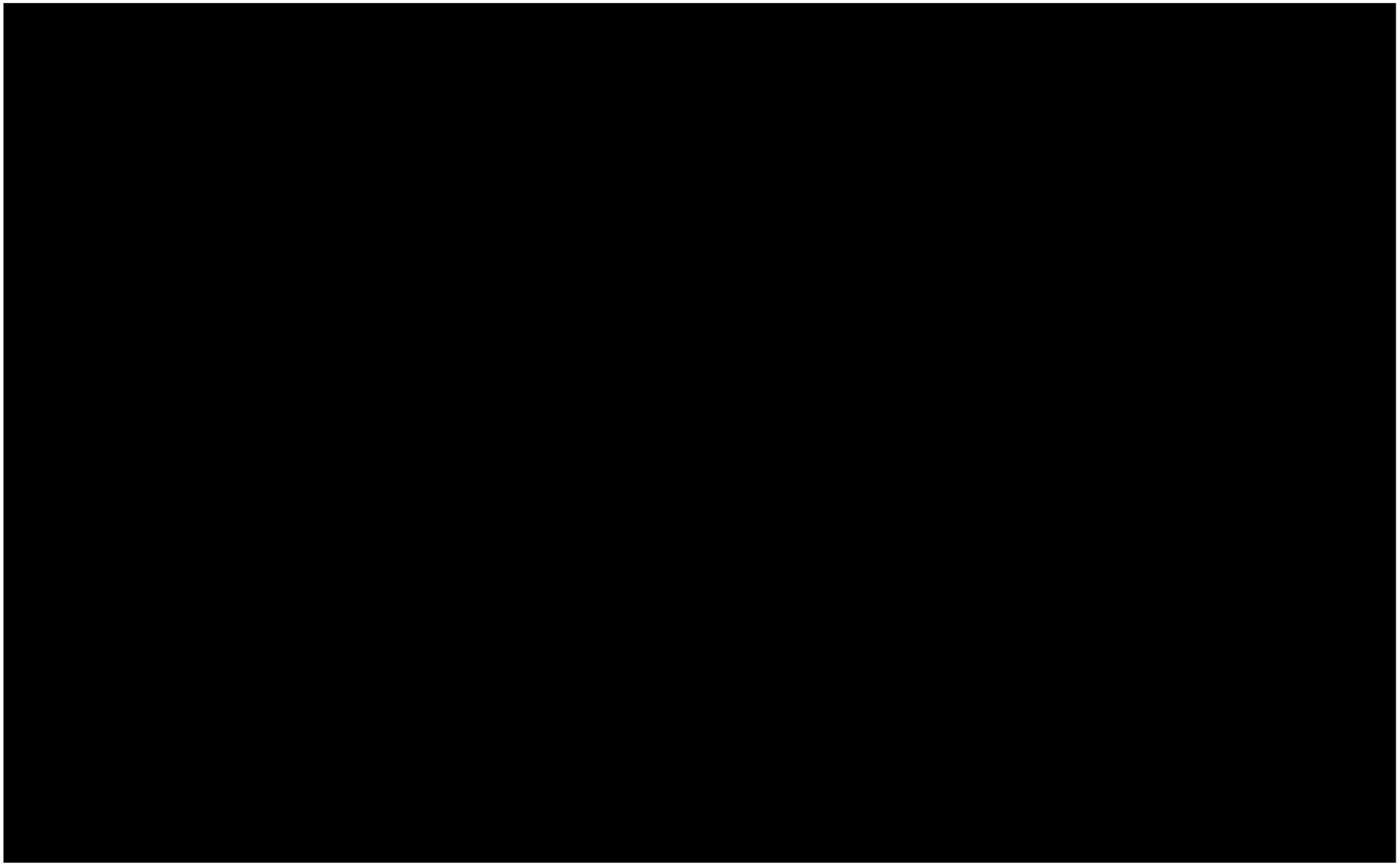
ADA = Anti-Drug Antibody for OPT-302; BCVA = Best Corrected Visual Acuity; DLT = Dose Limiting Toxicity; ETDRS = Early Treatment of Diabetic Retinopathy Study; FA = Fluorescein Angiography; PK = Pharmacokinetic; SD-OCT = Spectral Domain Optical Coherence Tomography

[redacted]

[redacted]

[redacted]

[redacted]



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