

COVER LETTER

To:

ClinicalTrials.gov Protocol Registration and Results System (PRS) Review Team

Dear PRS Review Team,

On behalf of the study sponsor, Khyber Teaching Hospital, Peshawar, we are submitting the clinical trial record for review and registration in ClinicalTrials.gov.

Study title:

“Comparison of Suprachoroidal Bevacizumab versus Intravitreal Bevacizumab in Patients with Center-Involving Diabetic Macular Edema – A Randomized Controlled Trial”

This is a prospective, single-center, randomized, parallel-group interventional study comparing suprachoroidal bevacizumab with intravitreal bevacizumab in patients with center-involving diabetic macular edema. The planned total sample is 60 participants/eyes, with 30 allocated to each study group. Both groups are planned to receive bevacizumab 1.25 mg/0.05 mL at monthly intervals for three months. The principal outcomes are change in best-corrected visual acuity (BCVA) and central macular thickness (CMT), assessed at baseline and at four months.

The study is sponsored by Khyber Teaching Hospital, Peshawar, and has Institutional Review Board/ethics approval recorded as 485/IREB/KTH. The anticipated study start date previously provided was 1 October 2026, with primary completion anticipated in October 2027 and study completion in December 2027. These dates must be confirmed against the actual study status before submission.

We confirm that the information entered into the ClinicalTrials.gov record will be checked for accuracy and consistency with the approved protocol, ethics documentation, and study conduct. Any required corrections will be made in accordance with ClinicalTrials.gov requirements.

Thank you for your consideration.

Sincerely,

Principal Investigator

Date: 22/10/2026

STUDY PROTOCOL

Comparison of Suprachoroidal Bevacizumab versus Intravitreal Bevacizumab in Patients with Center-Involving Diabetic Macular Edema – A Randomized Controlled Trial

STUDY IDENTIFICATION

Study type: Interventional

Study design: Prospective, randomized, parallel-group, single-center trial

Allocation: Randomized

Intervention model: Parallel assignment

Masking: Assessor-masked (verify and specify exactly who is masked)

Primary purpose: Treatment

Study phase: Not applicable, if this is a non-phase drug study

Study location: Khyber Teaching Hospital, Peshawar, Pakistan

Sponsor: Khyber Teaching Hospital, Peshawar

Ethics/IRB approval reference: 485/IREB/KTH

Planned sample size: 60 participants/eyes, 30 per group

ClinicalTrials.gov identifier: To be assigned by ClinicalTrials.gov.

BACKGROUND AND RATIONALE

Diabetic macular edema (DME) is an important cause of visual impairment among people with diabetes. Anti-vascular endothelial growth factor (anti-VEGF) treatment is used to reduce macular edema and improve or preserve visual function. The route of administration may influence treatment response, procedural considerations, and adverse events. This trial is designed to compare suprachoroidal and intravitreal administration of bevacizumab in patients

with center-involving DME, using visual acuity and central macular thickness as key measures of treatment response.

OBJECTIVE

Primary objective:

To compare the change in best-corrected visual acuity (BCVA) from baseline to four months between patients treated with suprachoroidal bevacizumab and those treated with intravitreal bevacizumab.

Secondary objective:

To compare the change in central macular thickness (CMT) from baseline to four months between the two groups, and to describe and compare adverse events observed during the study.

STUDY HYPOTHESIS

The study will test whether the change in BCVA and CMT at four months differs between the suprachoroidal and intravitreal bevacizumab groups. The analysis will use two-sided tests unless the final protocol specifies otherwise.

STUDY SETTING AND DURATION

The study will be conducted at Khyber Teaching Hospital, Peshawar, Pakistan. The dates previously provided were:

- Anticipated study start: 1 October 2026
- Anticipated primary completion: October 2027
- Anticipated study completion: December 2027

These dates are planned dates and must be updated if recruitment or follow-up has started, or if the approved schedule differs.

STUDY POPULATION

The target population is patients diagnosed with center-involving diabetic macular edema who meet the final protocol's eligibility criteria and provide informed consent.

SAMPLE SIZE

The planned sample size is 60 participants/eyes, with 30 in each group. The previous study notes indicate that the calculation was performed using OpenEpi and that a 15% dropout allowance was considered. The final registration and protocol should state the outcome used for the calculation, assumptions, effect size, alpha, power, and any adjustment used. Verify that the final calculation supports 30 per group and that the unit of allocation and analysis (participant or eye) is explicitly defined.

RECRUITMENT AND CONSENT

Potentially eligible patients will be assessed against the approved eligibility criteria. The study team will explain the purpose, procedures, potential benefits, risks, alternatives, confidentiality protections, and voluntary nature of participation. Written informed consent will be obtained before any study-specific procedures. Participants may withdraw in accordance with the consent form and approved protocol.

RANDOMIZATION AND ALLOCATION

Participants will be assigned to one of two parallel groups:

- Group A: Suprachoroidal bevacizumab
- Group B: Intravitreal bevacizumab

STUDY INTERVENTIONS

Group A: Suprachoroidal bevacizumab

- Bevacizumab dose previously specified: 1.25 mg in 0.05 mL.
- Planned schedule: monthly injections for three months.

- Route: suprachoroidal.
- Administration must be performed by appropriately trained clinical personnel according to the approved protocol and institutional procedures.

Group B: Intravitreal bevacizumab

- Bevacizumab dose previously specified: 1.25 mg in 0.05 mL.
- Planned schedule: monthly injections for three months.
- Route: intravitreal.
- Administration must be performed by appropriately trained clinical personnel according to the approved protocol and institutional procedures.

OUTCOME MEASURES

Primary outcome:

- Change in best-corrected visual acuity (BCVA) from baseline to four months.

Secondary outcomes:

- Change in central macular thickness (CMT) from baseline to four months.
- Adverse events during the study period.

STUDY VISITS AND ASSESSMENTS

The previously supplied outline identifies baseline assessment and an outcome assessment at four months, with monthly treatment for three months. The approved visit schedule should specify the timing of:

- Screening and eligibility assessment
- Baseline clinical and ophthalmic assessment
- Each monthly injection visit
- Four-month outcome assessment

- Adverse-event assessment and any additional follow-up

SAFETY MONITORING

Adverse events and serious adverse events will be recorded, assessed, and managed according to the approved protocol and institutional policies. The protocol should define the adverse-event collection period, severity grading, seriousness criteria, relatedness assessment, reporting timelines, and the person responsible for reporting. Include specific ocular and systemic risks identified in the approved consent form and protocol. Do not claim that an independent data monitoring committee is present unless one has been appointed.

DATA COLLECTION AND CONFIDENTIALITY

Study data will be recorded in study forms and/or a secure electronic database. Participants will be assigned coded study identifiers. Direct identifiers will be kept separate from analytic data and access will be limited to authorized personnel. Data handling, storage duration, access, and sharing will follow institutional requirements and the approved protocol.

ETHICAL CONSIDERATIONS

The study has an ethics approval reference of 485/IREB/KTH, as previously provided. Confirm the full committee name, approval date, and approved protocol version before submission. Written informed consent will be obtained. Any protocol amendments will be submitted to the relevant ethics committee and updated in the ClinicalTrials.gov record when required.

DISCONTINUATION AND WITHDRAWAL

Participants may withdraw consent at any time. The investigator may discontinue study treatment when clinically necessary, for safety reasons, or according to the approved protocol. The protocol should specify whether data already collected may be retained and analyzed, and how participants who discontinue treatment will be followed.

DATA MANAGEMENT AND QUALITY ASSURANCE

Data will be checked for completeness, consistency, and plausibility. Corrections to source data and study records will be traceable. The study team will retain essential documents and maintain records according to institutional policy and applicable regulatory requirements.

STUDY TIMELINE

Previously supplied anticipated dates:

- Study start: 1 October 2026
- Primary completion: October 2027
- Study completion: December 2027

DISSEMINATION

Results may be disseminated through peer-reviewed publication and scientific presentations. Reporting will aim to be accurate and transparent, irrespective of whether findings favor either treatment group. ClinicalTrials.gov results reporting obligations and timelines should be followed if applicable.

STATISTICAL ANALYSIS PLAN (SAP)

PURPOSE

This Statistical Analysis Plan describes the planned analysis for the randomized comparison of suprachoroidal versus intravitreal bevacizumab in patients with center-involving diabetic macular edema. It should be finalized before analysis of outcome data and must remain consistent with the approved protocol and ClinicalTrials.gov record.

ANALYSIS POPULATIONS

Intention-to-treat (ITT) population:

All randomized participants will be analyzed in the group to which they were assigned, regardless of treatment received, where outcome data are available and consistent with the final protocol.

Per-protocol population:

A secondary analysis may include participants who complete treatment and follow-up without major protocol deviations, using prespecified criteria. Define these criteria before examining outcome results.

Safety population:

All participants who receive at least one study treatment will be included in the safety analysis and analyzed according to the treatment actually received, if this is consistent with the final protocol.

GENERAL STATISTICAL PRINCIPLES

- Statistical analyses will be performed using IBM SPSS Statistics version 26, as previously specified.
- All tests will be two-sided.
- A p-value below 0.05 will be considered statistically significant.
- Estimates will be reported with 95% confidence intervals where appropriate.
- Continuous variables will be summarized using mean and standard deviation when reasonably normally distributed, or median and interquartile range when skewed.
- Categorical variables will be summarized as frequencies and percentages.
- Distributional assumptions and outliers will be assessed before selecting parametric tests.
- The analysis will prioritize effect estimates and confidence intervals rather than relying only on p-values.

BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics will be summarized by randomized group. Continuous variables will be presented as mean (SD) or median (IQR), and categorical variables as n (%). Baseline significance testing will not be used to determine whether randomization was successful; any observed imbalances will be described and considered in sensitivity or adjusted analyses where justified.

PRIMARY OUTCOME ANALYSIS: BCVA

The primary endpoint is change in BCVA from baseline to four months, measured on the scale specified in the final protocol.

For each participant, change will be calculated as:

Change in BCVA = BCVA at four months – BCVA at baseline.

The direction of improvement depends on the scale used; interpretation must state this explicitly. The between-group difference in change will be estimated with a 95% confidence interval. If change scores are approximately normally distributed and assumptions are met, an independent-samples t-test may be used. If assumptions are materially violated, an appropriate nonparametric method may be used. An analysis of covariance (ANCOVA), with four-month BCVA as the dependent variable and baseline BCVA and treatment group as explanatory variables, may be preferable for the primary analysis if prespecified and appropriate to the design.

SECONDARY OUTCOME ANALYSIS: CMT

Change in CMT from baseline to four months will be calculated as:

Change in CMT = CMT at four months – CMT at baseline.

The between-group difference in change will be estimated with a 95% confidence interval. An independent-samples t-test may be used for normally distributed change scores with appropriate assumptions; otherwise, use a prespecified suitable alternative. An ANCOVA model adjusting for baseline CMT may be used if specified in the final analysis plan. Report units, effect estimate, 95% CI, and exact p-value.

ADVERSE EVENTS

Adverse events will be tabulated by group using counts and percentages. Where suitable, the proportion of participants experiencing at least one adverse event will be compared using a chi-square test or Fisher's exact test, depending on expected cell counts. Serious adverse events and clinically important ocular events will be described individually in accordance with confidentiality requirements. The study is not expected to be powered to detect rare safety events; results will be interpreted accordingly.

MISSING DATA

The extent and reasons for missing baseline and follow-up measurements will be summarized by group. The primary analysis approach to missing outcome data must be prespecified. Do not automatically replace missing values with the last observation carried forward. If feasible and appropriate, use a model-based approach or multiple imputation under stated assumptions. A complete-case analysis may be presented as a sensitivity analysis. The handling of participants who withdraw or receive incomplete treatment must follow the approved protocol.

MULTIPLICITY

BCVA is the designated primary outcome. CMT and adverse-event outcomes are secondary. Unless a formal multiplicity adjustment is prespecified, secondary outcome p-values will be interpreted as supportive/exploratory rather than as confirmatory evidence. If the study intends confirmatory claims for multiple endpoints, specify the adjustment procedure in advance.

COVARIATE-ADJUSTED ANALYSIS

If justified and prespecified, adjusted analysis may include baseline values of the relevant outcome and a limited number of clinically important covariates defined before analysis. With a total planned sample of 60, the number of covariates should remain limited to avoid overfitting. Covariates must not be selected solely on the basis of observed p-values.

SUBGROUP AND SENSITIVITY ANALYSES

No confirmatory subgroup analyses are specified in the information currently available. Any subgroup analyses should be limited, clinically justified, and prespecified. Potential sensitivity analyses include a per-protocol analysis and an analysis using an alternative appropriate method for missing data. Clearly label analyses not prespecified in the final protocol as exploratory.

SAMPLE SIZE AND POWER

The planned sample size is 60 participants/eyes (30 per group), with the prior notes indicating an OpenEpi calculation and a 15% dropout allowance. The final SAP/protocol should provide the exact assumed difference, standard deviation or event proportions, alpha, power, calculation method, and adjustment for anticipated dropout. These values should be copied from the actual sample-size calculation; they must not be fabricated.

PRESENTATION OF RESULTS

Results will be presented in tables and/or figures showing:

- Participant flow and numbers randomized, treated, followed up, and analyzed in each group
- Baseline characteristics by group
- Baseline and four-month BCVA, plus change from baseline
- Baseline and four-month CMT, plus change from baseline
- Adverse events by group
- Effect estimates with 95% confidence intervals and exact p-values where appropriate

SOFTWARE

IBM SPSS Statistics version 26.