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Title Page

Protocol Title: A Phase IV interventional post approval trial to assess the safety of intravitreal aflibercept for the treatment of diabetic macular edema (DME) in patients in India.

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Short Title: India IPAT (PASS) IVT aflibercept in DME

Study Phase: IV

Sponsor Name and Legal Registered Address: Bayer AG, 51373 Leverkusen, Germany

Regulatory Agency Identifier Number(s): Not applicable

Protocol Date: 8 JUN 2023

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This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

PPD **and contact information** PPD PPD

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Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 2 (Technical)	*3.0*	*8 JUN 2023*	*Consolidated version created to reflect changes as mentioned in Protocol Amendment History below (technical amendment)*
Amendment 1 (Technical)	*2.0*	*07 APR 2022*	*Consolidated version created to reflect changes as mentioned in Protocol Amendment History below (technical amendment)*
Clinical Study Protocol	*1.0*	*20 DEC 2021*	*Version approved by the HA and used in the study*

Protocol Amendment Summary of Changes Table

Amendment 2: 8 JUN 2023

This amendment is prepared to include **already approved** country-specific changes into a unique consolidated protocol version.

Overall Rationale for the Amendment:

Brief rationale provided for the relevant sections below.

Section # and Name	Description of Change	Brief Rationale
Page 1: Sponsor Name and Legal Registered Address	Change in Sponsor name and address from **Bayer Zydus Pharma Private Limited**, Central Avenue, Hiranandani Estate, Thane – 400607, Maharashtra, India to **Bayer AG**, 51373 Leverkusen, Germany	Typo error noted. Sponsor name in the previous protocol is Bayer Zydus Pharma Private Limited. Actual resgistered sponsor for this study is Bayer AG.
Page 1: Country Medical Lead / Medical Monitor	Included change in Country Medical Lead/ Medical Monitor for the study	Included details of new Country Medical Lead/ Medical Monitor

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase IV interventional post approval trial to assess the safety of intravitreal aflibercept for the treatment of diabetic macular edema (DME) in patients in India.

Short Title: India IPAT (PASS) intravitreal aflibercept in DME

Rationale:

The proposal for approval of intravitreal aflibercept (EYLEA) in DME indication was submitted to the Health Authority (HA) of India. CCI [redacted] Therefore, this Phase IV interventional study is designed to assess the safety of intravitreal aflibercept in routine clinical practice in India in patients diagnosed with DME as the primary objective.

Among the currently available therapies in India, laser and steroid therapies have their own limitations in terms of limited visual acuity gain specifically with laser therapy and increased risk of clinically important side effects. There is a need for a treatment that can not only stabilize but also clinically relevantly improve and maintain vision in patients with DME using a regimen that minimizes the burden to patients.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To investigate the safety of intravitreal aflibercept for the treatment of diabetic macular edema (DME) in a phase IV setting	• Frequency (number) of ocular and non-ocular TEAEs
Secondary	
• To investigate the efficacy of use of intravitreal aflibercept for the treatment of diabetic macular edema (DME) in a phase IV setting	• The change in best corrected visual acuity (BCVA) from baseline to week 52, as assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart or equivalent. • Change in central retinal thickness (CRT) from baseline to week 52 as measured by optical coherence tomography (OCT), FA • Proportion of eyes that gain ≥ 5, 10 and 15 ETDRS letters from baseline to Week 52. • Proportion of eyes with a ≥2 step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score

Overall Design:

Disclosure Statement:

This study is a phase IV, interventional, open label, single-arm, prospective, multi-centre study, to investigate the safety of intravitreal aflibercept for the treatment of DME in Indian patients at a dosage of 2 mg according to label with the primary endpoint assessed at Week 52.

Number of Participants:

Approximately 100 patients will be recruited in the study at approximately 10-15 study sites.

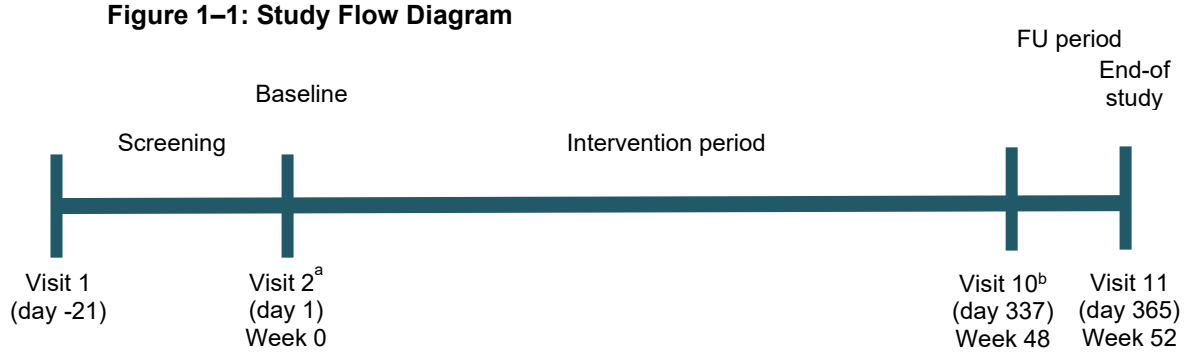
Study steering committee:

A study steering committee, including HCPs and Investigators, will be set up locally at Bayer Zydus. The study steering committee will meet periodically to review safety data as needed.

1.2 Schema

This study is composed of the following periods: Screening, treatment, and follow-up (FU). Participants will be considered "on study" during screening, treatment, and FU periods. An overview of the study schema is presented in Figure 1–1.

Figure 1–1: Study Flow Diagram



[a]The first dose of study intervention
[b]The last dose of study intervention

1.3 Schedule of Activities (SoA)

Study assessments and procedures are presented by study period and visit in Table 1–1.

Table 1–1: Schedule of Activities (SoA)

Study Procedure	Screening	Screening + Day 1[1]	Intervention Period									Active FU visit	Early Discontinuation FU visit (+4 weeks)[8]
Visit	**1**	**1 + 2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**-**
Week	**-**	**0**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	
Day	**-21 to -1**	**1±3**	**1±3**	**29±7**	**57±7**	**85±7**	**113±7**	**169±7**	**225±7**	**281±7**	**337±7**	**365±7**	**-**
Informed consent	X	X											
Demographic information	X	X											
Inclusion and exclusion criteria	X	X	X										
Physical examination[4]	X	X										X	X
Medical/ ophthalmic history	X	X											
Current medical/ophthalmic conditions	X	X											
Serum pregnancy test (WOCBP only)[1]	X												
Urine pregnancy test (WOCBP only)[1]			X	X	X	X	X	X	X	X	X	X	X
PT & PTT	X	X						X				X	X
Haematology[6]	X	X						X				X	X
Chemistry panel[6]	X	X						X				X	X
HbA1c[6]	X	X				X		X	X	X	X		
Urine analysis[6,7]	X	X						X				X	X
12-lead ECG	X	X										X	X
Vital signs[5, 11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study intervention[12]		X	X	X	X	X	X	X	X	X	X		
Ocular assessments[10]													
Visual acuity (ETDRS, bilateral)	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X	X	X

Indirect ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X
FP/ FA	X[9]	X						X				X	X
Safety assessments (ocular and non-ocular events)													
AE review[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE review[2]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X
Safety FU (phone call)[3]		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE: adverse event; ECG: electrocardiogram; ETDRS: Early Treatment Diabetic Retinopathy Study; FA: fluorescein angiography; FP: fundus photography; FU: Follow-up; HbA1c: haemoglobin A1c; IOP: intraocular pressure; OCT: optical coherence tomography; PT: prothrombin time; PTT: partial thromboplastin time; SAE: serious adverse event; WOCBP: women of child-bearing potential.

1. Visits 1 and 2 can be combined, except for WOCBP. Serum pregnancy results are required to determine eligibility. If a participant is not of childbearing potential and screening/baseline visit is to be combined, all procedures listed for both visits must be performed, except for the serum pregnancy test. In addition, all women of childbearing potential (WOCBP) will have a urine pregnancy test at each visit starting at visit 2 (day 1). A negative urine pregnancy test is required before treatment is administered.
2. An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention. Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, will be recorded as an AEs. An AE arising or worsening after the start of study treatment administration until 30 days after the last administration of study treatment, will be considered a treatment-emergent adverse event (TEAE).
3. Safety FU telephone calls will be made 16 to 36 hours after each visit to ensure that no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred. Calls will be made after each visit starting at visit 2. Alternatively, the investigator may schedule an additional safety FU visit for the day after treatment.
4. Physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded at screening.
5. Participant's blood pressure and pulse will be measured after the participant has been sitting for 5 minutes.
6. After screening visit, blood and urine samples must be collected prior to study drug injection.
7. At visits at which FA is performed, urinalysis samples will be collected before FA in order to avoid false elevations in urine protein values.
8. If a participant withdraws from the trial before the end of trial (early discontinuation), he/she should undergo all end of study procedures and assessments after a follow-up period of 4 weeks.
9. FP/FA may be performed at Visit 1 or Visit 2; images must be reviewed by the investigator to confirm eligibility prior to randomization.
10. All ocular assessments must be reviewed by the investigator to confirm eligibility prior to the start of the study intervention.
11. Temperature, blood pressure, and pulse will be measured.
12. Participants will receive one aflibercept injection (2 mg; equivalent to 50 µL solution for injection) per month (every four weeks) for five consecutive doses, followed by one injection every alternate month (every 8 weeks) for rest of the duration.

2. Introduction

Increasing prevalence of diabetes mellitus is a major public health concern globally, especially in middle-income countries such as in India. Diabetes mellitus now affects 77 million adults in India, which is likely to increase to over 130 million by 2045 (Kulkarni et al. 2021; Gilbert et al. 2020).

Systemic and ocular complications of diabetes affect individuals in their most productive years of life (Kulkarni et al. 2021). Diabetic retinopathy (DR) is a well-known microvascular complication of diabetes mellitus and DME is the most common cause of vision loss in those with DR (Fong et al. 2004; Klein et al. 1984; Moss, Klein, and Klein, 1998). DME, a manifestation of DR, is a complex disease of multifactorial origin and is the most frequent cause of blindness in young and mid-aged adults in the developed world (Stefansson et al. 2000).

Global epidemiologic studies have shown that approximately 1 in 3 persons with diabetes has DR, and 1 in 10 has proliferative diabetic retinopathy (PDR) or DME. Based on these rates, between 100 million and 120 million people have DR and possibly 20 million to 30 million have PDR or DME (Wong et al. 2018; Ozturk 2014). Prevalence of DR in India ranges from 17.6% to 28.2% and less than 10% of the persons with diabetes suffer from DME or PDR (Kulkarni et al. 2021).

Many different therapies are available for the treatment of DME, reflecting its multifocal pathogenesis. Previously, laser photocoagulation was the standard of care for DME management after the ETDRS demonstrated it was effective in 1985. However, over the past several years, intravitreal injection of anti-VEGF (human vascular endothelial growth factor) agents has surpassed laser photocoagulation as the first-line treatment for DME because randomized clinical trials have demonstrated the superiority of intravitreal anti-VEGF therapy in achieving greater visual acuity outcomes compared to laser photocoagulation. Intravitreal anti-VEGF agents are effective because they block the abnormally elevated levels of VEGF that lead to excessive vascular permeability and neovascularization (Li et al. 2020).

Aflibercept is a recombinant fusion protein, comprising portions of VEGF receptor (VEGFR)-1 and VEGFR-2 extracellular domains that are fused to the Fc portion of human IgG1. The innovative multitargeted trap of aflibercept is the only anti-VEGF that blocks all VEGFR-1 ligands, including VEGF and placental growth factor (Carle et al. 2013; Prescribing Information, EYLEA 40 mg/mL). Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kDa and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells (Prescribing Information, EYLEA 40 mg/mL).

2.1 Study Rationale

The proposal for approval of IVT aflibercept (EYLEA) in DME indication was submitted to the Health Authority (HA) of India. CCI [redacted]

Therefore, this Phase IV interventional study is designed to assess the safety of IVT aflibercept (EYLEA) in routine clinical practice in India in patients diagnosed with DME as the primary objective.

There is an urgent need to identify and treat DME optimally in India. A recent study reported the prevalence of any DME to be 8.9% and that of referable DME as 2.4% of the total Indian diabetic population of 77 million. Considering conservative estimate of 2% diabetic population having DME, likely magnitude of treatable DME is 15,40,000 persons (Kulkarni et al. 2019; Das et al. 2016). Vision impairment and blindness from DR and DME will increase unless systems and services are put in place with an increased access to diagnosis and effective treatment (Gilbert et al. 2020).

The standard of care for DME treatment has gradually shifted from macular laser photocoagulation to anti-VEGF injections with more options becoming available over the years. Real-world studies have shown that around 7-8 anti-VEGF injections per year have desirable impact on centre involving DME (Kulkarni et al. 2021). Intravitreal anti-VEGF therapy is now accepted worldwide as the current gold standard for the treatment of centre involving DME (Kelkar et al. 2020). The therapy has been shown to be effective and safe in the treatment of DME in numerous randomized clinical trials with improvements in visual acuity and reductions in retinal thickness (Li et al. 2020).

The 3 most commonly used intravitreal anti-VEGF agents are aflibercept, ranibizumab, and bevacizumab. Efficacy and safety of IVT aflibercept in the DME indication has already been established globally based on positive results from two pivotal Phase III trials, VIVID and VISTA (refer to Section 2.2 and Section 2.3). In a pivotal, large, parallel-arm, randomized study conducted by "The Diabetic Retinopathy Clinical Research Network," aflibercept has been found to be superior to bevacizumab and ranibizumab for participants with lower vision, whereas differences between the three drugs were unimportant for participants with better vision in a 1-year outcome. Visual acuity outcomes at 2 years were also similar for eyes with better baseline VA with all the three agents. Among eyes with worse baseline VA (20/50 to 20/320), aflibercept continued to show superior 2-year VA outcomes compared with bevacizumab; and comparable outcome with better safety to ranibizumab.

Real-world studies have also demonstrated the efficacy of aflibercept. A prospective cohort study (n = 147) from France published in 2020 showed that aflibercept was associated with improved functional and anatomical outcomes in both treatment-naïve and previously treated patients with DME. After 12 months, treatment-naïve patients gained a mean of +7.8 EDTRS letters and previously treated patients gained +5.0 letters. There was also a decrease in mean CST in both groups. Another 2-year retrospective study (n = 30) from Greece that was published in 2019 showed that using aflibercept in DME patients was highly effective, with significant increase in median logarithm of the minimum angle of resolution (logMAR) BCVA and lower CST compared to baseline (Li et al. 2020).

Intravitreal Aflibercept (EYLEA; Bayer) is a product approved by the FDA and EMA since 2014 for the treatment of visual impairment due to DME. The product is approved for the treatment DME in over 105 countries and has the potential to address the unmet need for patients in India with DME.

2.2 Background

The efficacy of VEGF inhibitors has been examined and proven in numerous clinical trials. These agents have the potential not only to stabilize but also to improve visual function and are considered the standard of care (SoC) for visual impairment due to DME. Whilst the first generation of anti-VEGF treatments have undoubtedly improved patient's outcomes, the requirement for regular injections and monthly monitoring have been a huge burden on patients, their caregivers, physicians, and the healthcare system in general. Aflibercept is a

potent, specific VEGF inhibitor with a high affinity for all isoforms of VEGF and placental growth factor.

Efficacy and safety of IVT aflibercept in the DME indication has already been established globally based on positive results from two pivotal Phase III trials: VIVID (406 patients) and VISTA (461 patients), which also included Asian patients. The VIVID and VISTA studies provide the first head-to-head comparisons of anti-VEGF blockade alone versus laser therapy alone (Korobelnik et al. 2014). Results from these pivotal trials demonstrate that IVT aflibercept given either every 4 or every 8 weeks (after 5 initial monthly doses) is superior to laser and results in both significant visual acuity (VA) gains and prevention of severe VA loss. The primary efficacy endpoint (change from baseline in best corrected visual acuity [BCVA] at 52 weeks) was superior in both IVT aflibercept arms (2 mg every 4 weeks, and 2 mg every 8 weeks after 5 initial monthly doses), compared with the laser group in both studies. The percentage of eyes in the laser group that lost ≥15 letters of vision was 9.1% in VISTA and 10.6% in VIVID, replicating the 10% loss in the laser group reported in the literature. Overall, the 1-year results of the VISTA/VIVID studies demonstrated that IVT aflibercept significantly improves visual outcomes and significantly decreases severe vision loss, while simultaneously improves the diabetic retinopathy severity score, compared with focal laser photocoagulation (Korobelnik et al. 2014).

A pivotal, large, parallel-arm, randomized study conducted by “The Diabetic Retinopathy Clinical Research Network” compared the relative efficacy and safety of IVT aflibercept, bevacizumab, and ranibizumab in the treatment of DME [DRCRnet Protocol T]. One-year outcomes found aflibercept to be superior to bevacizumab and ranibizumab for participants with lower vision, whereas differences between the three drugs were unimportant for participants with better vision. When the initial VA letter score was 78 to 69 (equivalent to approximately 20/32 to 20/40) (51% of participants), the mean improvement was 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab ($P > 0.50$ for each pairwise comparison). When the initial letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab ($P <0.001$ for aflibercept vs. bevacizumab, $P = 0.003$ for aflibercept vs. ranibizumab, and $P = 0.21$ for ranibizumab vs. bevacizumab). There were no significant differences among the study groups in the rates of serious adverse events (SAEs), hospitalization, death, or major cardiovascular events (Wells et al. 2015). VA outcomes at 2 years were also similar for eyes with better baseline VA with all the three agents. Among eyes with worse baseline VA (20/50 to 20/320), aflibercept continued to show superior 2-year VA outcomes compared with bevacizumab; and comparable outcome with better safety to ranibizumab: mean improvement was 18.3, 13.3, and 16.1 letters, respectively (aflibercept vs. bevacizumab, $P = 0.02$; aflibercept vs. ranibizumab, $P = 0.18$; ranibizumab vs. bevacizumab, $P = 0.18$) (Wells et al. 2016).

Based on these results, a Cochrane review on anti-VEGFs in DME has also concluded that IVT aflibercept confers an advantage over ranibizumab and bevacizumab in people with DME at 1 year in visual and anatomic outcomes; similar inference was also drawn by a further network metanalysis incorporating individual participant data (Virgili et al. 2018; Muston et al. 2018). International guidelines viz. the European Society of Retina Specialists (EURETINA) and evidence-based treatment recommendations for DME for the Asian countries also recognize the advantages of IVT aflibercept for the treatment of visual impairment due to DME and reinforce the superiority of IVT aflibercept over other anti-VEGF agents in participants with baseline VA of less than 69 letters (worse than 20/50) (Schmidt-Erfurth et al. 2017;Cheung et al. 2018).

2.3 Benefit/Risk Assessment

The participants for this study will be included from government and private hospitals across geographies in India to be representative of the population with DME in India.

As discussed in Section 2.2, the safety and efficacy of IVT aflibercept in the DME indication has already been established globally based on positive results from Phase III trials (VIVID and VISTA), a pivotal study DRCRnet Protocol T, a Cochrane review, a meta-analysis, and EURETINA guidelines.

Aflibercept has been generally well tolerated when administered by IVT injection. The adverse event (AEs) and SAEs that have been reported during the clinical development programs are consistent with the rates that have been reported with other IVT administered VEGF inhibitors. These events are often attributable to either the IVT injection procedure, the demographics of the patient population, or to progression of the disease being treated (Investigator's Brochure).

A total of 2,501 participants have been treated with the recommended dose of 2 mg aflibercept across eight Phase III studies. Table 2–1 displays all ARs (serious and non-serious) from eight Phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product (Investigator's Brochure).

Table 2–1: All Treatment-Emergent Adverse Drug Reactions Reported in Patients in Phase III Studies

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity[a]	
Eye disorders	Conjunctival hemorrhage, Eye pain	Retinal pigment epithelial tear[b], Detachment of the retinal pigment epithelium, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid edema, Injection site hemorrhage, Punctate keratitis, Conjunctival hyperemia, Ocular hyperemia	Endophthalmitis[c], Retinal detachment, Retinal tear, Uveitis, Iritis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Anterior chamber flare, Corneal edema	Cataract traumatic, Vitritis, Hypopyon

[a]During the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions

[b]Conditions known to be associated with neovascular AMD. Observed in the neovascular AMD studies only.

[c]Culture positive and culture negative endophthalmitis

Source: Investigator's Brochure

Serious adverse reactions (ARs) related to the injection procedure have occurred in less than 1 in 2,400 IVT injections with aflibercept and included endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous detachment and intraocular pressure increased (Investigator's Brochure).

The most frequently observed adverse reactions (in at least 5% of patients treated with aflibercept) were conjunctival haemorrhage (25.0%), eye pain (10.2%), cataract (7.6%) intraocular pressure increased (7.5%), vitreous detachment (7.4%), and vitreous floaters (6.9%) (Investigator's Brochure).

IVT injections, including those with aflibercept, have been associated with endophthalmitis. Nevertheless, the cases can be minimized by employing proper aseptic injection technique while administering aflibercept and can be managed appropriately by counselling the participants to report any symptoms suggestive of endophthalmitis without delay (Prescribing Information, EYLEA 40 mg/mL).Prescribing Information, EYLEA 40 mg/mL).

Increases in intraocular pressure (IOP) have been seen within 60 minutes of an IVT injection, including with aflibercept. A special precaution is required in patients with poorly controlled glaucoma, and such patients are not intended to be enrolled in this study (Prescribing Information, EYLEA 40 mg/mL).

There are no data on the use of aflibercept in pregnant women. Studies in animals have shown reproductive toxicity after systemic administration. The pregnant women are not intended to be enrolled in this study (Prescribing Information, EYLEA 40 mg/mL).

All the participants in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the study. However, study participation does not guarantee a direct or indirect benefit for the participant. Safety will be ensured by monitoring the participants for AEs both clinically and by laboratory testing.

The planned study incorporates standard clinical procedures that are used in Phase IV studies with DME. The study design is supported, and study execution will be followed by a Steering Committee of experts to ensure participant safety on an ongoing basis (refer Section 4.1.3).

All participants in this trial will be treated in accordance with best SoC in compliance with guidelines and recommendations. Relevant emerging safety data, e.g., SAEs, suspected unexpected serious adverse reactions (SUSARs), and serious safety-related protocol deviations, will be communicated as soon as possible between the sponsor, all study sites and investigators and trial participants.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of aflibercept may be found in the Investigator’s Brochure (IB) and the Prescribing Information (PI).

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with aflibercept are justified by the anticipated benefits that may be afforded to participants with DME.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety of IVT aflibercept for the treatment of DME in a phase IV setting	• Frequency (number) of ocular and non-ocular TEAEs
Secondary	
• To investigate the efficacy of use of IVT aflibercept for the treatment of DME in a phase IV setting	• The change in BCVA from baseline to week 52, as assessed using the ETDRS chart or equivalent. • Change in CRT from baseline to week 52 as measured by OCT, FA • Proportion of eyes that gain ≥ 5, 10 and 15 ETDRS letters from baseline to Week 52. • Proportion of eyes with a ≥2 step improvement in the ETDRS DRSS score

4. Study Design

4.1 Overall Design

This study is a phase IV, interventional, open label, single-arm, prospective, multi-centre study, to investigate the safety of IVT aflibercept for the treatment of DME in Indian participants in routine clinical practice in India at a dosage of 2 mg according to label with the primary endpoint assessed at Week 52. The trial will be conducted at approximately 10-15 study sites across India. Approximately 100 participants will be recruited in the study.

4.1.1 Study visits

The study duration will be up to 13 months covering 11 visits:

- Screening period (Visit 1 [Day-21 to Day-1]): The start of the study period is defined by signing of the informed consent form (ICF).
- Baseline visit (Visit 2 [Day 1]): HbA1c and ocular assessments check have to be confirmed at the baseline visit before the intravitreal administration of aflibercept.
- Visits 1 and 2 can be combined (as Visit 1+2) except in women of childbearing potential (see Section 1.3). Participants who met all of the inclusion and none of the exclusion criteria, will be assigned to aflibercept treatment on Day 1, Week 0 (at Visit 2 or Visit 1+2).
- Treatment period (Visit 2 [Day 1, Week 0] to Visit 10 [Day 337, Week 48]) that include study intervention per month for five consecutive doses (Visit 2-6), followed by one injection every alternate month for rest of the duration (Visit 7-10).
- FU period: from month 11 to month 12 (visit 11)

Once patients complete Visit 11/Week 52, can be switched over to commercially available supply or other suitable treatment options at the discretion of the Investigator (see Section 6.6).

4.1.2 Selection of Study or Fellow Eye

Only 1 eye per patient will be enrolled in the study (Section 6.8).

For patients who meet eligibility criteria in both eyes, the eye with the worst VA will be selected as the study eye. If a patient has DME with similar BCVA in both eyes, the eye with the clearest media will be selected as the study eye. If the ocular media of both eyes are similar in clarity, the patient's non-dominant eye (if identifiable) will be selected as the study eye. If neither eye is dominant, the right eye will be designated as the study eye. For treatment of the fellow eye, see Section 6.8.

4.1.3 Study Committees

Study steering committee

A study steering committee, which is composed of a panel of experts in the field including HCPs and Investigators, will be set up locally at Bayer Zydus that will meet periodically to review safety data as needed. These data may include, but are not limited to:

- Treatment-Emergent Adverse Events (TEAEs) that result in an early study withdrawal. A TEAE is defined as any event arising or worsening after the start of study treatment administration until 30 days after the last administration of study treatment.
- SAEs
- Selected laboratory tests, as deemed appropriate by the study steering committee
- Specific AEs as defined by the SMT, such as cardiovascular AEs

Appropriate action, if needed, will be taken based upon this review and in consultation with the medical monitor.

4.2 Scientific Rationale for Study Design

Please refer to Section 2.1 for the study rationale.

CCI [redacted]

The intervention model of the study includes single group assignment of IVT aflibercept in an open-label fashion. It is justified to not use any comparator or masking in the study as the primary objective of the study is to collect additional safety data for IVT aflibercept in Indian patients with DME. The efficacy of aflibercept is well-established in global clinical trials and real-world studies, and therefore the data for changes in BCVA scores and CRT will be collected as the secondary objective. The study will adhere to standard provisions of an interventional study like drug supply, defined sample size, treatment/dosing schedule per label, safety follow-ups, and AE reporting.

4.3 Justification for Dose

The participants in the study will receive one aflibercept injection (2 mg; equivalent to 50 µL solution for injection) per month (every four weeks) for five consecutive doses, followed by one injection every alternate month (every 8 weeks) for rest of the duration. This dosage regimen is as per the label (prescribing Information) approved by the HA of India.

4.4 End of Study Definition

The end of the study (EOS) is defined as the date when the last visit of the last participant has been achieved in all participating centres.

Last participant last visit (LPLV) of a participant is reached if he/she has completed the last scheduled visit shown in the SoA (this also includes phone contacts during long-term FU) unless the participant withdrew consent or is lost to FU.

Furthermore, to reach EOS, all participants should have discontinued aflibercept treatment.

At the EOS visit (Visit 11), the study participant can be switched over to commercially available supply or other suitable treatment options at the discretion of the Investigator.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

The study will be conducted in 100 participants across 10-15 centres in India. Participants will be included from government and private hospitals across geographies in India to be representative of the population. At each study centre, not less than 70% of the participants should be naïve. The logistics will be applied in the electronic data capture (EDC) system to identify the patient as naïve or pre-treated, and to alert the investigator when the naïve and pre-treated patients cap is reached at the study centre.

Participants who did not receive any previous/ prior treatment (i.e., participants that previously have not been treated with IVT anti-VEGF or steroids) within the last 3 months of the Day 1 of the study, without laser treatment, and without ocular surgery of the study eye are considered as naive.

The target study population is men and women 18 years and older with DME secondary to diabetes mellitus involving the centre of the macula (central subfield on OCT that is defined as circular area of 1 mm diameter around the centre point of fovea). Participants must meet all eligibility criteria at screening and baseline visits; however, participants do not need repeat assessments if the screening and baseline visits are combined (see SoA). Refer to Section 5.4 to refer to re-screening criteria. If a subject fails screening, i.e., does not meet all inclusion criteria or meets 1 or more of the exclusion criteria, the participants can be re-screened. If the screen failure is due to an inability to meet the BCVA inclusion criterion, at least 30 days since the previous assessment must pass before re-screening of BCVA. A patient can be re-screened upto two times as long as he meets the re-screening criteria.

5.1 Inclusion Criteria

A participant must meet the following criteria at screening and day 1 to be eligible for inclusion in the study:

1. Female or male adult participant ≥18 years of age, with type 1 or 2 diabetes mellitus.
2. Participant must have DME secondary to diabetes mellitus, involving the centre of the macula (defined as the area of the centre subfield of OCT) in the study eye.
3. Decrease in vision, determined to be primarily the result of DME in the study eye.
4. Retinal thickness of ≥300 µm in the study eye, as assessed by OCT.
5. BCVA ETDRS letter score of 73 to 24 (i.e., VA of 20/50 to 20/320) or equivalent in

the study eye.

6. Participant for whom the decision to initiate treatment with IVT aflibercept has been made by the treating Investigator/Physician.
7. Willing and able to comply with clinic visits and study-related procedures.
8. Provide a signed ICF prior to any study procedures.

5.2 Exclusion Criteria

A participant who meets any of the following criteria at either the screening visit or day 1 will be excluded from the study:

1. Having any contraindications to the use of IVT aflibercept as listed in the local prescribing information (i.e., ocular or periocular infection, active severe intraocular inflammation, and known hypersensitivity to aflibercept or to any of the excipients).
2. History of vitreoretinal surgery and/or scleral buckling in the study eye.
3. Ocular conditions with a poorer prognosis in the fellow eye than in the study eye.
4. Known history of allergy to fluorescein used in fluorescein angiography, and indocyanine green used in indocyanine green angiography. As indocyanine green dye contains iodine, so severe allergic reactions are possible in patients allergic to iodine.
5. Any laser photocoagulation (panretinal or macular) in the study eye within the last 3 months of Day 1.
6. Any cataract surgery in the study eye within the last 3 months of Day 1.
7. Any intraocular surgery in the study eye within the last 3 months of Day 1.
8. Received previous/ prior treatment as mentioned below:
    a) Received anti-VEGF drugs in the study eye (pegaptanib sodium, bevacizumab, ranibizumab, etc., including aflibercept) within the last 3 months of Day 1.
    b) Received IVT dexamethasone or triamcinolone in the study eye within the last 3 months of Day 1.
    c) Received intraocular or periocular corticosteroids in the study eye within the last 4 months of Day 1.
    d) Had fluocinolone implant in the study eye within the last 3 years of Day 1.
    e) Had dexamethasone implant in the study eye within the last 6 months of Day 1.
    f) systemic anti-angiogenic agents within 6 months of Day 1.
9. Uncontrolled glaucoma in the study eye (patient who has had filtration surgery in the past, or likely to need filtration surgery in the future).
10. IOP ≥25 mm Hg in the study eye.
11. Only 1 functional eye even if that eye is otherwise eligible for the study.
12. Ocular media of insufficient quality to obtain fundus and OCT images.
13. Uncontrolled DM in the opinion of the investigator.
14. Uncontrolled blood pressure (BP) (defined as systolic >160 mm Hg or diastolic >95 mm

Hg while patient is sitting).

15. History of cerebrovascular accident or MI within 6 months of Day 1.
16. Renal failure, dialysis, or history of renal transplant.
17. Participated in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device.
18. Pregnant or breast-feeding women.
19. Sexually active men or WOCBP[a] who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly or diaphragm plus contraceptive sponge, foam, or jelly).
20. WOCBP[a] with either a positive pregnancy test result or no pregnancy test at baseline.

5.3 Lifestyle Considerations

No restrictions are required.

5.4 Screen Failures

A screen failure occurs when a participant consents to participate in the clinical study but is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Whether the participant can repeat the screening will be discussed with the Sponsor. Sponsor's approval of re-screening for a participant must be documented. If the screen failure is due to an inability to meet the BCVA inclusion criterion, at least 30 days since the previous assessment must pass before re-screening of BCVA. A patient can be re-screened upto two times times as long as the re-screening criteria are met.

Also, for re-screening, the participant has to re-sign the ICF, even if it was not changed after the participant's previous screening. The screening failure will be registered in Interactive Voice/Web Response System (IxRS) to close the patient identification number (PID), and re-screening will start again by signing a new ICF and being assigned a new PID via IxRS.

5.5 Criteria for Temporarily Delaying Enrollment/Study Intervention

Not applicable for this protocol.

[a]Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention Administered

Participants will receive one aflibercept injection (2 mg; equivalent to 50 µL solution for injection) per month (every four weeks) for five consecutive doses, followed by one injection every alternate month (every 8 weeks) for rest of the duration.

The injection will be administered by a qualified physician experienced in administering IVT injections. Immediately following the IVT injection, the participant will be monitored for elevation in IOP. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following IVT injection, the participant will be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Table 6–1: Study Intervention(s) Administered

Intervention Label	Aflibercept
Intervention Name	Eylea
Intervention Description	Each vial provides a usable amount to deliver a single dose of 50 microliters containing 2 mg aflibercept. Aflibercept treatment is initiated with one injection per month (every four weeks) for five consecutive doses, followed by one injection every two months (8 weeks).
Type	Drug
Dose Formulation	Vial
Unit Dose Strength(s)	IVT injections of 50 µL (2 mg) of aflibercept
Dosage Level(s)	2 mg aflibercept and initiated with one injection per month (every four weeks) for five consecutive doses, followed by one injection every two months (8 weeks)
Route of Administration	IVT injection
Use	Experimental
Packaging and Labeling	Study intervention will be provided in vial. Each vial will be labeled as required per country requirement

6.2 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Study intervention should be stored in a refrigerator and at the recommended label temperature (2°C to 8°C / 35.6°F to 46.4 °F) in vial in the outer carton in order to protect from light.

The vial is for single use in one eye only. The recommended dose for Eylea is 2 mg aflibercept (equivalent to 50 microlitres solution for injection). The study drug will be withdrawn using aseptic techniques through an 18-gauge filter needle attached to a 1-mL syringe. The filter needle will be discarded after withdrawal of the vial contents and should not be used for IVT injection. The filter needle should be replaced with a 30G x 1/2-inch injection needle for the IVT injection. The contents in the syringe should be expelled until the plunger is aligned with the line that marks 0.05 mL on the syringe. It is recommended to visually inspect the solution for injection prior to administration. The vial is not to be used if particulates, cloudiness, or discoloration are visible. Prior to usage, the unopened vial of aflibercept may be stored at room temperature (25 °C / 77°F) for up to 24 hours. After opening the vial, proceed under aseptic conditions..

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are not applicable for this study.

This is an open-label study and all open label intervention at all visits must be assigned by the IxRS for tracking and accountability purpose.

Patient identification

After a participant has signed the PI/ICF, the patient identification number will be provided to the investigators through an IxRS. Participants will be identified by a 9-digit patient identification number consisting of:

Digits 1 to 5 = Unique centre number

Digits 6 to 9 = Current patient number within the centre

The IxRS procedure is described in detail in a separate IxRS instruction manual that will be maintained in the electronic trial master file (eTMF) and in each centre’s investigator site file.

6.4 Study Intervention Compliance

The administration of IVT aflibercept will be performed in the clinic for 5 monthly treatments (5 loading doses) followed by treatment every 8 weeks. The date and time of each injection administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). Reasons for dose delay or infusion interruption will also

be recorded in the source data and in the eCRF. The drug accountability will be managed through IxRS.

The participants will receive study intervention directly from the investigator or designee at the site, under medical supervision. The dose of study intervention, study participant identification, and study eye (right/left) will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Dose Modification

This study does not permit changes in the study regimen.

6.6 Continued Access to Study Intervention after the End of the Study

At the end-of-study visit (Visit 11), the study participant can be switched over to commercially available supply or other suitable treatment options at the discretion of the Investigator.

6.7 Treatment of Overdose

Overdosing with increased injection volume may increase IOP. Therefore, in case of an overdose, IOP should be monitored, and if deemed necessary by the investigator/treating physician, adequate treatment should be initiated.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 30 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

For more details, refer to prescribing information of Eylea.

6.8 Prior and concomitant Therapy

6.8.1 Prior and concomitant medications

All medications taken before study start (initiated and stopped before first intravitreal aflibercept injection) are termed prior medications. Prior medications meeting the criteria listed below have to be documented:

- Considered relevant for the study indication (DME) such as:
    - Intravitreal injections with steroids (inclusive of steroid implants) or other VEGF inhibitors
    - Peribulbar injections with steroids or other VEGF inhibitors

- Treatments for any of the concomitant diseases of interest
- Other ophthalmological treatments

All medications taken in addition to aflibercept for any indication (either initiated at the time of enrollment or during the study) are termed concomitant medications.

Information to be collected for medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, application route, indication and, if applicable, the eye(s) treated.

Please note that any action during the study performed for the fellow eye is to be recorded as concomitant medication.

6.8.2 Prior and concomitant surgeries/laser treatments

Prior surgeries are considered relevant to the study indication and have to be documented:

- Macular laser treatment
- Pan retinal or focal retinal laser treatment
- Ocular surgeries

All ocular surgeries after the first aflibercept injection are termed concomitant surgeries.

For surgeries, the name of the surgery, the date, the reason, and the eye operated have to be recorded.

6.8.3 Prohibited Medications

Participants may not receive any medications (approved or investigational) for their DME in the study eye other than the assigned study treatment as specified in this protocol, until they have completed the end of study (week 52) visit assessments or assessments after the early discontinuation of study intervention.

This includes medications administered locally (e.g., IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically, with the intent of treating the study and/or fellow eye.

For IVT treatment of the fellow eye, other anti-VEGF agents will not be allowed unless aflibercept is not available due to logistical reasons. However, bevacizumab will not be permitted.

6.8.4 Permitted Medications

If the fellow eye has DME involving or threatening the centre of the macula, starting at week 4 (Visit 3), participant may receive treatment with aflibercept 2 mg using a dosing regimen of 5 initial monthly doses, followed by 2q8. The fellow eye treatment will not utilize clinical supply for the study eye. Other anti-VEGF agents will not be allowed unless aflibercept (Eylea) is not available due to logistical reasons. The participant can receive the commercially available anti-VEGF for the treatment of fellow eyes, and in such case, the medication will not be supplied by the Sponsor.

However, bevacizumab will not be permitted.

The participant’s fellow eye may receive treatment on the same day as the study eye or at an unscheduled visit. All fellow eye treatments must be recorded on the eCRF as a concomitant medication and/or procedure for the fellow eye. The fellow eye will not be considered an additional study eye. Participants who receive treatment for the fellow eye will not be

required to be withdrawn from the study. Safety of the fellow eye will be monitored, and all AEs will be collected. Other conditions in the fellow eye may be treated with approved therapies.

Any other medication that are considered necessary for the participant's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

6.8.5 Rescue Medicine

Not applicable for this protocol.

6.8.6 Additional Treatment

Patients will be evaluated for additional treatment starting at week 24 at the discretion of the investigator. Criteria for additional treatment (at least 1 criterion must be met):

- Loss at any single visit of ≥15 letters from the best previous VA score due to DME and the patient's current VA score is not better than the baseline score.
- Loss at 2 consecutive visits at least 7 days apart (second visit may be an unscheduled visit) of ≥10 letters from the best previous VA score due to DME and the patient's current VA score is not better than the baseline score.

The participants who qualify for additional treatment, will receive an active laser treatment at the current visit, and will continue with aflibercept at the current and all future visits.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Unnecessary withdrawal of subjects from the study should be avoided and all efforts should be taken to motivate subjects to adhere to all study procedures until the end of the trial.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study until end of active FU period which is referred to as early discontinuation visit (4 weeks post permanent discontinuation of study intervention). See the SoA for the data to be collected at the early discontinuation FUvisit.

The reason for study drug interruption or permanent study drug discontinuation/ withdrawn from the study should be recorded in the eCRF and in the subject's medical records.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. Refer to SoA for data to be collected and evaluations to be completed at the time of early discontinuation.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow Up

A participant will be considered lost to FU if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to FU, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

Best Corrected Visual Acuity (BCVA)

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters at each study visit. VA examiners and BCVA examination lane must be certified to ensure consistent

measurement of BCVA. The procedure for conducting BCVA and measurement for BCVA must be in the same throughout the study at each site.

Slit Lamp Examination

Participants' anterior eye structure and ocular adnexa will be examined at each study visit using a slit lamp by the investigator. The procedure for conducting slit lamp examination must be in the same throughout the study at each site.

Intraocular Pressure (IOP)

IOP of the study eye will be measured at every visit using a calibrated Goldmann applanation tonometry or Tono-pen™. The same method of IOP measurement must be used in each participant throughout the study. IOP will be measured pre-dose and at approximately 30 minutes post-dose. The physician (or designee) will measure IOP pre-injection (bilateral), and approximately 30 minutes post-injection (study eye).

A more detailed description for IOP can be found in PI.

Indirect Ophthalmoscopy

Participants' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) and post-dose (study eye). Post-dose evaluation must be performed immediately after injection (active drug or sham).

Optical Coherence Tomography (OCT)

Retinal characteristics will be evaluated at every visit using spectral domain OCT. Starting with the screening visit (visit 1), images will be captured for both eyes. OCT technicians must be qualified to ensure consistency and quality in image acquisition. OCT images will be read by the investigator/ qualified reader at the site. All OCTs will be electronically archived at the study sites as part of the source documentation. OCT machine and image setting for OCT must be in the same throughout the study at each site.

Fundus Photography/Fluorescein Angiography (FP/ FA)

The anatomical state of the retinal vasculature will be evaluated by FP and FA. The study eye will be the transit eye. FP and FA will be captured for both eyes. Photographers must be qualified to ensure consistency and quality in image acquisition. FP and FA images will be read by the investigator/qualified reader at the site. All FPs and FAs will be archived at the site as part of the source documentation. FP/ FA machines and image setting for FP/FA must be in the same throughout the study at each site.

FP and FA evaluations will be performed at screening (visit 1 or visit 2), week 24, and week 52. FA must also be performed whenever any laser re-treatment criterion is met, and at least 12 weeks have passed since the last laser or sham laser.

8.2 Safety Assessments

Investigators should refer to the Safety Information section of the current IB for the expected side effects including unexpected AEs and hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

Safety will be assessed by monitoring and recording all AEs and SAEs, cardiac, hematologic and blood chemistry parameters, vital signs, ECG, and any abnormal findings observed during the performance of physical examinations.

Planned timepoints for all safety assessments are provided in the SoA.

Therapeutic monitoring should be performed following dose modification of study drug in a manner consistent with the local clinical SoC. In general, participants should be closely monitored for adverse drug reactions of all concomitant medications regardless of the path of drug elimination.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g., clotted or haemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the Investigator will be informed to determine FU activities outside of this protocol.

Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 8.3). Additional assessments may be indicated at any time during the course of the study at the discretion of the Investigator. In addition, lab tests may be repeated at the discretion of the Investigator, if clinically indicated.

8.2.1 Physical Examinations

A full physical examination will be performed by the investigator or qualified designee at screening and at the end-of-study. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

8.2.2 Vital Signs

Participant’s vital signs will be measured at screening visit and at every study visit.

Vital signs will be measured in a sitting position after 5 minutes rest with a completely automated device and will include temperature, systolic and diastolic BP, and pulse. Three readings of BP and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

Single 12-lead ECG(s) will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Pregnancy Testing

Serum and urine pregnancy tests are performed at Screening and during treatment. Specific time points can be found in the SoA. The frequency of pregnancy tests may be higher, if required by local regulations. More details can be found in Section 10.4.

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The intensity of AEs should be documented using the NCI-CTCAE, v5.0.

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Drug delayed
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

The definitions of AEs and SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative [LAR]).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Investigators should refer to the Safety Information section of the current IB of aflibercept for the expected side effects. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the end of FU visit at the timepoints specified in the SoA. SAEs which are related to protocol-required study procedures (e.g., SAE related to invasive study procedures) will be recorded as SAEs from the signing of the ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention will be recorded as an AE.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs , will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to FU (as defined in Section 7.3). Further information on FU procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB/Prescribing Information and will notify the IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of follow up period.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect FU information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study, will discontinue study intervention or be withdrawn from the study.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.3.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable for this protocol.

8.3.7 Adverse Events of Special Interest

Not applicable for this protocol.

8.3.8 Medical Device Deficiencies

Not applicable for this protocol.

8.4 Pharmacokinetics

Pharmacokinetics and pharmacodynamic parameters are not evaluated in this study.

8.5 Genetics and/or Pharmacogenomics

Not applicable for this protocol.

8.6 Biomarkers

Not applicable for this protocol.

8.7 Immunogenicity Assessments

Not applicable for this protocol.

8.8 Health Economics or Medical Resource Utilization and Health Economics

Health economics *or* medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to study database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

A final analysis will be performed after the EOS which is the date the analytical dataset is completely available.

9.1 Statistical Hypotheses

There is no hypothesis to confirm or reject in this study.

9.2 Analysis Sets

The primary population for the efficacy analysis is the Full analysis set (FAS) population that will be comprised of all participants assigned to study intervention (aflibercept injection).

The population for the safety analysis is the safety analysis set (SAF) population that will be comprised of all participants who received at least one dose of study intervention (aflibercept injection).

The FAS is used to analyse endpoints related to the efficacy objectives and the SAF is used to analyse the endpoints and assessments related to safety.

9.3 Statistical Analyses

9.3.1 General Considerations

All outcomes will be analysed descriptively by either frequency tables or summary statistics for the total study population. Whenever meaningful, continuous variables will also be categorized. If applicable, the analysis will be stratified by baseline factors.

All analyses will be performed for each of the following cohorts:

- Naïve
- Pre-treated

and for the total study population.

9.3.2 Primary Endpoints Analysis

AEs will be summarized for the SAF using the MedDRA coding system. Occurrence rates for single AEs will be calculated based on the total number of patients valid for safety and 95% confidence intervals (CIs) will be provided. AEs will be categorized according to ocular or non-ocular nature, relatedness, seriousness, discontinuation of therapy, action taken and outcome.

The analyses will be performed on incident TEAE. Events which are not treatment-emergent will be tabulated without further stratification. Events are considered as TEAE, if they started after 1st IVT-aflibercept injection and not later than 30 days after last IVT- aflibercept injection. Laboratory data will be listed only.

Further details will be specified in the statistical analysis plan (SAP).

9.3.3 Secondary Endpoints Analysis

All secondary outcomes will be analysed by frequency tables or summary statistics such as mean, standard deviation, minimum, percent quartiles, median, maximum and 95% confidence intervals for the total population. Whenever meaningful, continuous variables will also be categorised.

Summary statistics for absolute BCVA values and respective changes from baseline will be displayed. For sensitivity analysis, an analysis of covariance (ANCOVA) model with baseline BCVA as covariate will be performed to estimate the baseline adjusted BCVA change. No formal comparison will be made.

More details will be provided in the SAP.

9.3.4 Other Analysis

Further sensitivity analyses like subgroup analysis by baseline BCVA will be performed. BCVA values cut-off for groups division for subgroup analysis: VA letter score ranging from78 to 69, or 20/32 to 20/40 Snellen; and those with fewer than 69 letters, equivalent to about 20/50 or worse. Details on subgroup analyses will be specified in the SAP.

Frequency (number) of IVT aflibercept injections in the study eye over 12 months of the study period will be provided with 95% CI.

Further sensitivity analysis which take lost to follow up into consideration will be applied (like TEAE incidence rates per person years and TEAE incidence rates per injections) and will be described in the SAP.

9.4 Interim Analysis

No formal interim analysis is planned in this study.

9.5 Sample Size Determination

The study aims to enrol 100 patients from 10-15 sites.

The sample size of 100 patients CCI [redacted] to describe the safety profile of the study intervention. In an analysis of the data from the clinical trials VIVID and VISTA, the reported proportion for any ocular SAE was 1.7% over the course of 52 weeks. Table 9–1 shows the precision that might be expected in terms of 95% CIs for different AE proportions and 100 patients.

Table 9–1: Estimated 95% confidence intervals for different ocular serious adverse events proportions for N=100 patients

Assumed AE proportion	95% confidence interval	Width
1%	(0%, 5.4%)	5.4%
2%	(0.2%, 7%)	6.8%
3%	(0.6%, 8.5%)	7.9%
4%	(1.1%, 9.9%)	8.8%
Clopper-Pearson Confidence Intervals, PASS Version 13.0.11		

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IEC by the investigator and reviewed and approved by the IEC before the study is initiated.

Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH GCP and national and international regulations.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

All relevant information on the study will be summarized in an integrated patient information sheet and ICF provided by the Sponsor or the study centre.

Sample patient information and ICFs are provided as documents separate to this protocol.

Based on this patient information sheet, the Investigator or designee will explain all relevant aspects of the study to each participant prior to his/her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The Investigator will also mention that written approval of the IEC has been obtained.

Each participant will be informed about the following aspects of premature withdrawal:

Each participant has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

The participant’s data that have been collected until the time of withdrawal will be retained and statistically analysed in accordance with the SAP.

Participant-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analysed in accordance with the SAP. The participant has the right to object to the generation and processing of this post-withdrawal data. The participant’s oral objection may be documented in the participant’s source data.

Each participant will have ample time and opportunity to ask questions:

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participants or their LAR, and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their LARs will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participants or their LAR.

10.1.4 Data Protection

All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Study Steering Committee

The main task of study steering committee, which is composed of a panel of experts in the field including HCPs and Investigators, is to support the conduct of the study and to advise the Sponsor on clinical, medical, and scientific questions. Details of the committee will be specified in the Steering Committee charter.

10.1.6 Dissemination of Clinical Study Data

The Sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov. All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other Investigators. Regarding public disclosure of study results, the Sponsor will fulfill its obligations according to all applicable laws and regulations. The Sponsor is interested in the publication of the results of every study it performs.

The Sponsor recognizes the right of the Investigator to publish the results upon completion of the study. However, the Investigator, whilst free to utilize study data derived from his/her centre for scientific purposes, must obtain written consent of the Sponsor on the intended publication manuscript before its submission. To this end, the Investigator must send a draft of the publication manuscript to the Sponsor within a time period specified in the contract. The Sponsor will review the manuscript promptly and will discuss its content with the Investigator to reach a mutually agreeable final manuscript.

Result Summaries of Bayer's sponsored clinical trials in drug development Phases II, III, and IV and Phase I studies in participants are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers participant-level clinical trial data, study-level clinical trial data, and protocols from clinical

trials in participants for medicines and indications approved in the US and European Union (EU) on or after January 01, 2014, as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided .

The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan/contracts.

The data collection tool for this study will be a validated electronic data capture system. Participant data necessary for analysis and reporting will be transmitted into a validated database or data system.

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet-based EDC software system/Bayer system. Bayer will ensure that extensive software logics are applied to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secured host facility and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the EDC system will be through a password-protected security system. All internal Bayer and external Investigator site personnel seeking access must go through a thorough EDC software training before they are granted access to the EDC for use in Bayer's clinical studies. Training records are maintained.

The EDC System will contain a system-generated audit trail to capture any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information will be available both at the Investigator’s site and at Bayer.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The Contract Research Organization (CRO) is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the Source Data Location List (SDLL) or equivalent.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The principal Investigator of each centre must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, Sponsor) before participant recruitment may start at the respective centre. Likewise, all amendments to

the protocol must be signed by the principal Investigator and must have received all required external approvals before coming into effect at the respective centre.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or FU.

10.1.10 Publication Policy

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other Investigators. Regarding public disclosure of study results, the Sponsor will fulfil its obligations according to all applicable laws and regulations. The Sponsor is interested in the publication of the results of every study it performs.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in
- Table 10–1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters			
Haematology	Platelet count Red blood cell (RBC) count Haemoglobin Haematocrit	<u>RBC indices:</u> Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) %Reticulocytes	<u>White blood cell (WBC) count with differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (fasting or nonfasting)	Calcium	Alkaline phosphatase[2]	HbA1c
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]			

Table 10–1: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters

NOTES:

[1] Details of liver chemistry stopping criteria and required actions and FU are given in Section [7.1.1 Liver Chemistry Stopping Criteria] and Section [10.6 Liver Safety: Suggested Actions and FU Assessments [and Study Intervention Rechallenge Guidelines]]]. All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT [or AST] ≥3 × ULN and international normalized ratio (INR) >1.5 (if INR measured) which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

[2] If alkaline phosphatase is elevated, consider fractionating.

[3] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IEC

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.
- Treatment-Emergent Adverse Event (TEAE): A TEAE is defined as any event arising or worsening after the start of study treatment administration until 30 days after the last administration of study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. Results in death

b. Is life threatening

- The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Bayer in lieu of completion of the AE/SAE eCRF/required form.
  - There may be instances when copies of medical records for certain cases are requested by Bayer. In this case, all participant identifiers, with the exception

of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Bayer. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to Bayer.
- The investigator may change his/her opinion of causality in light of FU information and send an SAE FU report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- Immune-mediated adverse events (IMAEs) are AEs consistent with an immune mediated mechanism or immune-mediated component for which non-inflammatory aetiologies (e.g., infection or tumour progression) have been ruled out. IMAEs can include events with an alternate aetiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's eCRF.
- Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Bayer to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized FU period, the investigator will provide Bayer with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to Bayer within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Bayer will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the PVCH by telephone.
- Contacts for SAE reporting can be found in Safety Management Plan (SMP) and ICF.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming premenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:

a) Documented hysterectomy

b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

d) For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2 Contraception Guidance

WOCBP are excluded from the study (refer section 5.2).

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.)If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective - failure rate of ≥ 1% per year. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Abbreviations and Definitions

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
APTC	Anti-Platelet Trialists' Collaboration
AR	Adverse Reaction
AST	Aspartate aminotransferase
ATE	Arterial thrombotic event
BCVA	Best Corrected Visual Acuity
BP	Blood pressure
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CRT	Central Retinal Thickness
CTCAE	Common Terminology Criteria for Adverse Event
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRSS	Diabetic Retinopathy Severity Scale
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EMA	European Medicine Agency
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
eTMF	Electronic trial master file
EU	European Union
EURETINA	European Society of Retina Specialists
FA	Fluorescein angiography
FAS	Full analysis set
FDA	Food and Drug Administration
FP	Fundus photography
FU	Follow-up
GCP	Good Clinical Practice
HA	Health Authority
HbA1c	Haemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HEOR	Health Economics and Outcomes Research
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMAE	Immune-mediated adverse events
INN	International Nonproprietary Name
INR	International normalized ratio
IOP	Intraocular pressure
IUD	Intrauterine device
IVT	Intravitreal
IxRS	Interactive Voice/Web Response System
LAR	Legally Authorized Representative
LPLV	Last Participant Last Visit
MAH	Marketing Authorization Holder
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NCI	National cancer institute
OCT	Optical Coherence Tomography
PDR	Progressive Diabetic Retinopathy
PI	Prescribing information
PID	Patient identification number
PT	Prothrombin time
PTT	Partial thromboplastin time
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limits
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDLL	Source Data Location List
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SMP	Safety Management Plan
SMT	Safety monitoring team
SoA	Schedule of Activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-Emergent Adverse Event
ULN	upper limit of normal
US	United States
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White blood cell
WHO DD	World Health Organization Drug Dictionary
WOCBP	Women of child-bearing potential

11. References

Published References

Carle, M.V., Chu, T.G., Tabandeh, H. and Boyer, D.S., 2013. IVT aflibercept use in the treatment of macular edema from central retinal vein occlusion. Expert Review of Ophthalmology, 8(3), pp.227-235.

Cheung, G.C., Yoon, Y.H., Chen, L.J., Chen, S.J., George, T.M., Lai, T.Y., Park, K.H., Tahija, S.G., Uy, H.S. and Wong, T.Y., 2018. Diabetic macular oedema: evidence-based treatment recommendations for Asian countries. Clinical & experimental ophthalmology, 46(1), pp.75-86.

Das, T., Aurora, A., Chhablani, J., Giridhar, A., Kumar, A., Raman, R., Nagpal, M., Narayanan, R., Natarajan, S., Ramasamay, K. and Tyagi, M., 2016. Evidence-based review of diabetic macular edema management: Consensus statement on Indian treatment guidelines. Indian Journal of Ophthalmology, 64(1), p.14.

Fong DS, Aiello LP, Ferris FL III, Klein R, 2004. Diabetic retinopathy. Diabetes Care; 27 (1): 2540-2553.

Gilbert, C., Gordon, I., Mukherjee, C.R. and Govindhari, V., 2020. Guidelines for the prevention and management of diabetic retinopathy and diabetic eye disease in India: a synopsis. Indian journal of ophthalmology, 68(Suppl 1), p.S63.

Investigator's Brochure. VEGF Trap-Eye: IVT administration. Version 14. 2020.

Kelkar, A., Webers, C., Shetty, R., Kelkar, J., Labhsetwar, N., Pandit, A., Malode, M. and Tidke, S., 2020. Factors affecting compliance to intravitreal anti-vascular endothelial growth factor therapy in Indian patients with retinal vein occlusion, age-related macular degeneration, and diabetic macular edema. Indian Journal of Ophthalmology, 68(10), p.2143.

Klein, R., Klein, B.E., Moss, S.E., Davis, M.D. and DeMets, D.L., 1984. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Archives of ophthalmology, 102(4), pp.527-532.

Korobelnik, J.F., Do, D.V., Schmidt-Erfurth, U., Boyer, D.S., Holz, F.G., Heier, J.S., Midena, E., Kaiser, P.K., Terasaki, H., Marcus, D.M. and Nguyen, Q.D., 2014. IVT aflibercept for diabetic macular edema. Ophthalmology, 121(11), pp.2247-2254.

Kulkarni, S., Kondalkar, S., Mactaggart, I., Shamanna, B.R., Lodhi, A., Mendke, R., Kharat, J., Kapse, R., Dole, K. and Deshpande, M., 2019. Estimating the magnitude of diabetes mellitus and diabetic retinopathy in an older age urban population in Pune, western India. BMJ open ophthalmology, 4(1), p.e000201.

Kulkarni, S., Ramachandran, R., Sivaprasad, S., Rani, P.K., Behera, U.C., Vignesh, T.P., Chawla, G., Agarwal, M., Mani, S.L., Ramasamy, K. and Raman, R., 2021. Impact of treatment of diabetic macular edema on visual impairment in people with diabetes mellitus in India. Indian journal of ophthalmology, 69(3), p.671.

Li, A.S., Veerappan, M., Mittal, V. and Do, D.V., 2020. Anti-VEGF agents in the management of diabetic macular edema. Expert Review of Ophthalmology, 15(5), pp.285-296.

Moss, S.E., Klein, R. and Klein, B.E., 1998. The 14-year incidence of visual loss in a diabetic population. Ophthalmology, 105(6), pp.998-1003.

Muston, D., Korobelnik, J.F., Reason, T., Hawkins, N., Chatzitheofilou, I., Ryan, F. and Kaiser, P.K., 2018. An efficacy comparison of anti-vascular growth factor agents and laser photocoagulation in diabetic macular edema: a network meta-analysis incorporating individual patient-level data. BMC ophthalmology, 18(1), pp.1-11.

Ozturk BT, 2014. Who gets diabetic macular oedema; when; and why? Pathogenesis and risk factors. EMJ Diabet.; 2:105-111.

Schmidt-Erfurth, U., Garcia-Arumi, J., Bandello, F., Berg, K., Chakravarthy, U., Gerendas, B.S., Jonas, J., Larsen, M., Tadayoni, R. and Loewenstein, A., 2017. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica, 237(4), pp.185-222.

Stefánsson, E., Bek, T., Porta, M., Larsen, N., Kristinsson, J.K. and Agardh, E., 2000. Screening and prevention of diabetic blindness. *Acta Ophthalmologica Scandinavica*, *78*(4), pp.374-385.

Virgili, G., Parravano, M., Evans, J.R., Gordon, I. and Lucenteforte, E., 2018. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database of Systematic Reviews, (10).

Wells, J.A., Glassman, A.R., Ayala, A.R., Jampol, L.M., Aiello, L.P., Antoszyk, A.N., Arnold-Bush, B., Baker, C.W., Bressler, N.M., Browning, D.J. and Elman, M.J., 2015. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. The New England journal of medicine, 372(13), pp.1193-1203.

Wells, J.A., Glassman, A.R., Ayala, A.R., Jampol, L.M., Bressler, N.M., Bressler, S.B., Brucker, A.J., Ferris, F.L., Hampton, G.R., Jhaveri, C. and Melia, M., 2016. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology, 123(6), pp.1351-1359.

Wong TY, et al., 2018. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. Ophthalmology. 125(10): p. 1608-1622.

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