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## Vascular endothelial growth factor trap-eye (Aflibercept) for the management of diabetic macular edema

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### Abstract

Diabetic retinopathy (DR) is the most common cause of visual loss among working age individuals. Diabetic macular edema (DME) is an important complication of DR that affects around one third of the patients with DR. Several treatments have been approved for DME ranging from blood pressure and glycemic control to photocoagulation and more recently the use of vascular endothelial growth factor (VEGF) antagonists. The index review discusses aflibercept (EYLEA®-Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany) in the context of other VEGF antagonists currently available for the treatment of DME. A systematic search of literature was conducted on PubMed, Scopus, and Google Scholar with no limitation on language or year of publication. Pre-clinical studies of aflibercept have shown a higher affinity of this molecule for vascular endothelial growth factor A (VEGF-A) along with a longer duration of action as compared to other VEGF antagonists. Recent clinical trials have shown visual

outcome results for aflibercept to be similarly favorable as compared to other available agents with the added benefit of fewer required injections and less frequent monitoring. Aflibercept presents a potential exciting new addition to the armamentarium of current VEGF antagonists available for the treatment of DME and other retinal vascular diseases. However, further studies are indicated to confirm the role, safety, and efficacy of aflibercept for DME.

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**Key words:** Diabetic macular edema; Diabetic retinopathy; Anti-vascular endothelial growth factor agents; Vascular endothelial growth factor trap-eye; Aflibercept; EYLEA

**Core tip:** Several different agents have been approved recently for the treatment of diabetic macular edema (DME). The index article outlines the role of aflibercept, an anti-vascular endothelial growth factor (VEGF) agent, as a potential therapeutic option. Results from DME trials with aflibercept have been favorable and comparable to other anti-VEGF agents. Because of its longer half-life, aflibercept may also decrease the frequency of injections for DME patients. These results could be attributed to the stronger and prolonged binding of aflibercept to the VEGF-A receptor compared to other available antagonists. A better understanding of the effect of this drug in DME is expected once the phase 3 trial results are available.

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## INTRODUCTION

In recent years, the rise in the incidence of diabetes mellitus (DM) has been accompanied by a significant increase in the incidence of its microvascular complications, including diabetic retinopathy<sup>[1]</sup>. Diabetic retinopathy (DR) is the most common cause of visual loss in working age individuals in developed nations<sup>[2,3]</sup>. Complications of diabetic retinopathy include: cataract, glaucoma, macular edema (ME), retinal hemorrhage and retinal detachment, among others.

Approximately one third of DR patients have ME while overall ME affects around 7.5% of diabetic population<sup>[4]</sup>.

Over the years the treatment of DR has ranged from tight glycemic control to partial pituitary destruction and it was not until the Early Treatment Diabetic Retinopathy Study (ETDRS) showed efficacy of laser in treating DR/DME (Diabetic macular edema) that this modality was recognized as a useful intervention. It was demonstrated that laser photocoagulation can reduce the risk of moderate visual loss by 50% three years after initiation of treatment and was thus approved for the treatment of DME<sup>[5]</sup>. However, this form of treatment often prevents further visual loss and rarely results in improvement of vision. Therefore, researchers have explored newer therapies to improve treatment outcomes for patients with DME<sup>[6,7]</sup>.

## RATIONALE FOR CONSIDERING VEGF ANTAGONISTS FOR DME

DME results from microvascular changes secondary to hyperglycemia and the inflammatory changes associated with diabetes. These include thickening of the basement membrane and loss of pericytes, which leads to increased permeability of vessels leading to edema formation. Associated hypoxia due to vascular occlusion also leads to the release of several cytokines such as vascular endothelial growth factor (VEGF), insulin-like growth factor-1, angiopoietin-1 and angiopoietin-2, stromal-derived factor-1, fibroblast growth factor-2, and tumor necrosis factor<sup>[8]</sup>.

In 1994 Aiello *et al.*<sup>[9]</sup> demonstrated that VEGF levels are elevated in the ocular fluid of patients with diabetic retinopathy and other retinal disorders, including DME. Subsequently, Ozaki *et al.*<sup>[10]</sup> and Tolentino *et al.*<sup>[11,12]</sup> showed that intravitreal injection of VEGF in nonhuman primates could generate similar findings of diabetic retinopathy such as micro aneurysms, macular edema, and retinal neovascularization. Recent studies have also confirmed that hypoxia-induced VEGF release has a key role in the pathophysiology of DME<sup>[13]</sup>. During the past decade, the scientific community has learned that VEGF leads to neovascularization, increased vascular permeability and breakdown of the blood retina barrier, leading to the formation of ME<sup>[14]</sup>.

The establishment of the VEGF pathway leading to

ME in patients with diabetes and age-related macular degeneration (AMD) led to the development of anti VEGF therapies that are briefly discussed below.

## VEGF ANTAGONISTS THAT HAVE BEEN EVALUATED FOR DME

Pegaptanib sodium (Macugen, Eyetech Pharmaceuticals, Melville, NY/Pfizer, New York, NY) is an anti-VEGF aptamer that blocks the effect of VEGF by binding to the VEGF-A<sub>165</sub> isoform. It was the first United States Food and Drug Authority (FDA) approved anti-VEGF agent for treatment of choroidal neovascularization (CNV) resulting from AMD<sup>[15,16]</sup>.

Cunningham *et al.*<sup>[17]</sup> demonstrated in a double-masked phase 2 trial that subjects with DME who were assigned to the pegaptanib arm had better visual acuity (VA) outcomes [a larger proportion of those receiving 0.3 mg gained VAs of  $\geq 10$  letters as compared to the sham group (34% *vs* 10%,  $P = 0.003$ ) and  $\geq 15$  letters (18% *vs* 7%,  $P = 0.12$ )], were more likely to show reduction in central retinal thickness [Mean central retinal thickness decreased by 68  $\mu\text{m}$  with 0.3 mg, *vs* an increase of 4  $\mu\text{m}$  with sham ( $P = 0.02$ )], and were deemed less likely to need additional therapy with photocoagulation at follow-up as compared to sham injections at week 36. Phase 3 trials are currently underway<sup>[18]</sup>.

Ranibizumab (Lucentis<sup>TM</sup>, Genentech, San Francisco, CA) is a humanized antibody fragment that binds to all isoforms of VEGF-A. In 2006, Nguyen and colleagues were among the first clinician-scientists in the world to demonstrate that VEGF plays a critical role in the pathogenesis of DME and that employment of a VEGF antagonist such as ranibizumab may help to reduce retinal edema<sup>[19]</sup>. The READ-2 study, a phase II, randomized clinical trial, was conducted to evaluate the efficacy of ranibizumab for DME. Subjects were randomized 1:1:1 to receive 0.5 mg ranibizumab (group 1), focal or grid laser photocoagulation (group 2), or a combination of laser and ranibizumab (group 3). After the primary end point at month 6, at the discretion of the investigators, the majority of patients were treated only with ranibizumab. The mean improvement in BCVA was 7.24, 0.43, and 3.8 letters at the 6 mo primary end point<sup>[20]</sup>, compared with 7.7, 5.1, and 6.8 letters at month 24. Mean foveal thickness (FTH), defined as center subfield thickness, at month 24 was 340  $\mu\text{m}$ , 286  $\mu\text{m}$ , and 258  $\mu\text{m}$  for groups 1, 2, and 3, respectively<sup>[21]</sup>.

The RISE and RIDE studies, two randomized, multicenter and double masked phase 3 trials, have shown that ranibizumab improved vision and macular edema in patients with DME and reduced the risk of further visual loss. The results of the RISE study showed that 18.1% of sham patients gained  $\geq 15$  letters *vs* 44.8% of 0.3-mg ( $P < 0.0001$ ) and 39.2% of 0.5-mg ranibizumab patients ( $P < 0.001$ ). In RIDE, 12.3% of sham patients gained  $\geq 15$  letters *vs* 33.6% of 0.3-mg patients ( $P < 0.0001$ ) and 45.7%

of 0.5-mg ranibizumab patients ( $P < 0.0001$ ). Based on such significant results from RISE and RIDE, the FDA approved ranibizumab for DME in August 2012<sup>[22]</sup>.

Bevacizumab (Avastin®, Genentech, San Francisco, CA) is a full-length recombinant humanized antibody that targets all isoforms of VEGF-A. It is approved by the FDA as adjunctive treatment for metastatic colonic cancer but has not yet been approved for ocular diseases. The intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT) study, which was conducted on patients with center-involving clinically significant macular edema (CSME), showed a mean gain of 8.6 letters in the bevacizumab group as compared to a mean loss of 0.5 letters for the macular laser therapy group<sup>[23]</sup>.

Table 1 outlines a summary of landmark clinical trials in which VEGF antagonists were evaluated for DME.

## INTRODUCTION TO VEGF TRAP EYE/ AFLIBERCEPT

VEGF Trap-Eye/Aflibercept (EYLEA®-Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany) is a novel 115-kDa anti-VEGF agent. This fusion protein has been developed using the “trap technology” in which the extracellular binding domains of VEGF receptor (VEGFR) -1 and -2 are combined to the Fc segment of human immunoglobulin-G1 backbone<sup>[24]</sup>. Similar to ranibizumab and bevacizumab, aflibercept binds to all isomers of the VEGF-A family. Additionally, aflibercept binds to VEGF-B and placental growth factor; it is hypothesized that by blocking these factors, aflibercept may prove to be more efficacious<sup>[25]</sup>.

As a soluble circulation trap for VEGF, aflibercept binds firmly to the target, clears it out from the vitreous<sup>[26]</sup>, and consequently inhibits binding and activation of the VEGF receptors. The affinity of aflibercept to VEGF-A is much higher than monoclonal anti-VEGF antibodies (5 pM *vs* 1 pM kD).

The receptor sequences of aflibercept provide powerful VEGF binding (140 times that of ranibizumab) and the molecule's intermediate size of 110 kD (compared to 48 kD for ranibizumab and 148 kD for bevacizumab) creates a one-month intravitreal binding activity that exceeds both ranibizumab and bevacizumab<sup>[27]</sup>.

According to Stewart *et al.*<sup>[27]</sup>, a predictive model showed that aflibercept is active in the eye for 10 to 12 wk after a single intravitreal injection, with the binding activity of 2 mg VEGF Trap-Eye at 83 d estimated to be comparable to that of 0.5 mg ranibizumab at 30 d.

The half-life of intravitreally-administered aflibercept in animals is about 5 d; however, the half-life in the human eye has not yet been identified. Based on a mathematical model, this half-life is estimated to be about 7.13 d<sup>[28,29]</sup>.

### Dosage and safety

Aflibercept is available in a single-use vial which contains

0.05 mL of aflibercept (40 mg/mL in 10 mmol/L sodium phosphate, 40 mmol/L sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)<sup>[30]</sup>. To date, aflibercept is only available for intravitreal (IVT) injection. Although intravenous administration of doses  $\geq 1$  mg/kg has caused some systemic adverse events, no systemic effects have been reported in any phase-I, phase-II, or phase-III trials with IVT administration of doses of up to 4 mg ( $< 0.06$  mg/kg; 0.057 mg/kg)<sup>[31-33]</sup>.

## AFLIBERCEPT FOR DME: CURRENT EVIDENCE

In 2009, a phase-I study was conducted by Do *et al.*<sup>[31]</sup> to assess the safety, tolerability and bioactivity of a single 4 mg intravitreal injection of aflibercept in five patients with DME over a period of 6 wk. Participants older than 18 years with type 1 or type 2 diabetes, retinal thickening involving the foveal center due to DME, foveal thickness  $\geq 250$   $\mu$ m as measured by Stratus OCT, and BCVA between 20/40 and 20/320, were included in this study. The biological activity was measured by alterations in BCVA as well as changes in the retinal thickness assessed by OCT. The results of this trial established that a single intravitreal injection of 4 mg of aflibercept was well tolerated without any ocular toxicity. Its biologic activity was recognized by its role in improving BCVA and reducing retinal thickness. The median BCVA was 36 letters at baseline, and the median improvement seen was 9 letters after 4 wk and 3 letters after 6 wk. The median excess central 1mm foveal thickness (FTH) was 108  $\mu$ m at baseline, which was reduced to 59  $\mu$ m at 4 wk and 74  $\mu$ m at 6 wk after injection. Four of the five patients maintained the improvement in excess FTH (median 74 mm; 31% reduction from baseline,  $P = 0.0625$ ) at 6 wk after injection.

Based on the results of the phase I study, a 52 wk, multicenter, randomized, double-masked, active-controlled phase II clinical trial was conducted. The primary aim of the DME and VEGF Trap-Eye: INvestigation of Clinical Impact (DA VINCI) Study was to assess the safety and efficacy of intravitreal aflibercept in comparison with focal/grid laser photocoagulation in patients with DME. Diabetic patients who were  $\geq 18$  years old, with central retinal thickness (CRT)  $\geq 250$   $\mu$ m in the central subfield based on Stratus® OCT and with a BCVA between 20/40 and 20/320 were included in this study. Important study exclusion criteria were: history of vitreoretinal surgery, panretinal or macular laser photocoagulation within 3 mo of screening, use of intraocular or periocular corticosteroids within 3 mo of screening and uncontrolled diabetes mellitus or hypertension.

In the DA VINCI study, a total of 221 patients with DME from 39 sites in the United States, Canada, and Austria were randomly assigned in a 1:1:1:1:1 ratio to one of 5 treatment regimens in one eye only: 0.5 mg aflibercept every 4 wk (0.5q4); 2 mg aflibercept every 4 wk (2q4); 2 mg aflibercept for 3 initial monthly doses and then every 8 wk (2q8); 2 mg aflibercept for 3 initial monthly

**Table 1 Summary of some important trials in which vascular endothelial growth factor antagonists have been evaluated for diabetic macular edema**

Trial	Drug name						
	Pegaptanib	Bevacizumab	RESOLVE <sup>[40]</sup>	READ-2 <sup>[21,20]</sup>	READ-3	Ranibizumab	RIDE <sup>[22]</sup>
Study name	Study to Evaluate safety and tolerability of pegaptanib sodium in patients with diabetic macular edema <sup>[39]</sup>	BOLT study <sup>[23,39]</sup>	RESOLVE <sup>[40]</sup>	READ-2 <sup>[21,20]</sup>	READ-3	RISE <sup>[22]</sup>	RIDE <sup>[22]</sup>
Study type/phase	Interventional /phase 3	Interventional /phase 2	Interventional /phase 2	Interventional /phase 2	Interventional /phase 2	Interventional /phase 3	Interventional /phase 3
Number of patients	46	80	151	126	142	377	382
Intervention/study design	0.3 mg injections up to a maximum of 48 wk with a minimum-dosing interval of at least 6 wk	(1) Intravitreal Bevacizumab (2) MLT	(1) 0.3 mg Ranibizumab (2) 0.5 mg Ranibizumab (3) Sham	(1) 0.5 mg ranibizumab (group 1) (2) Focal/ grid laser (group 2) (3) 0.5 mg ranibizumab + focal/ grid laser (group 3)	(1) 0.5 mg ranibizumab (2) 2 mg ranibizumab	(1) Sham (2) 0.3 mg (3) 0.5 mg	(1) Sham (2) 0.3 mg (3) 0.5 mg
Results	No results available yet	Year 1 endpoint: A median gain of 8 ETDRS letters in the bevacizumab group <i>vs</i> a loss of 0.5 ETDRS letters in the MLT group ( $P = 0.0002$ ) CMT decreased from $507 \pm 145 \mu\text{m}$ to $378 \pm 134 \mu\text{m}$ ( $P < 0.001$ ) in the bevacizumab group, whereas it decreased from $481 \pm 121 \mu\text{m}$ to $413 \pm 135 \mu\text{m}$ in the MLT group ( $P = 0.02$ ) <sup>[39]</sup> Year 2 endpoint: A Mean gain of 8.6 letters for bevacizumab <i>vs</i> a mean loss of 0.5 letters in the MLT group <sup>[23]</sup> . A mean reduction of 146 $\mu\text{m}$ in the CMT in the bevacizumab arm <i>vs</i> 118 $\mu\text{m}$ in the MLT arm	A gain of $10.3 \pm 9.1$ letters with a loss of $1.4 \pm 14.2$ letters in the sham group ( $P < 0.0001$ ) A mean CMT reduction of $194.2 \pm 135.1 \mu\text{m}$ with ranibizumab and $48.4 \pm 153.4 \mu\text{m}$ with sham ( $P < 0.0001$ ) A gain of $\geq 10$ letters in BCVA from baseline in 60.8% of eyes in the ranibizumab group and 18.4% of eyes in the sham group ( $P < 0.0001$ )	The mean improvement in BCVA was 7.4, 0.5, and 3.8 letters at the 6 mo primary end point, compared with 7.7, 5.1, and 6.8 letters at month 24 in group 1, group 2 and group 3 respectively The percentage of patients who gained 3 lines or more of BCVA was 21, 0, and 6 at month 6, compared with 24, 18, and 26 at month 24. Mean FTH, defined as center subfield thickness, at month 24 was 340 $\mu\text{m}$ , 286 $\mu\text{m}$ , and 258 $\mu\text{m}$ for groups 1, 2, and 3, respectively	The study has completed Results are being analyzed	Year 2 endpoint: $\geq 15$ letters <i>vs</i> 44.8% of 0.3-mg ( $P < 0.0001$ ) and 39.2% of 0.5-mg ranibizumab patients ( $P < 0.001$ )	12.3% of sham patients <i>vs</i> 33.6% of 0.3-mg patients ( $P < 0.0001$ ) and 45.7% of 0.5-mg ranibizumab patients ( $P < 0.0001$ ) gained more than 15 letters

DME: Diabetic macular edema; MLT: Macular laser therapy; FTH: Foveal thickness; BOLT: The intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema; READ: The Ranibizumab for Edema of the mAcula in diabetes; CMT: Central macular thickness.

doses and then on an as-needed (PRN) basis (2PRN); or macular laser photocoagulation as specified by the modified ETDRS protocol. Assessments were done at baseline and every 4 wk thereafter.

The primary end point results of the DA VINCI

study (week 24) revealed that treatment with intravitreal aflibercept produced a statistically significant improvement in VA when compared with macular laser treatment. The four aflibercept groups showed a greater mean BCVA gain and decrease in CRT in comparison to the

**Table 2** Summary of clinical trials in which aflibercept was evaluated for diabetic macular edema

Trial	Study Name					
	Phase 1 study of VEGF trap in patients with DME	DA VINCI	VIVID-Japan	VISTA DME	VIVID-DME	Protocol T
Study type	Interventional	Interventional	Interventional	Interventional	Interventional	Interventional
Study phase	Phase 1	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3
Official title	An exploratory study of the safety, tolerability and biological effect of a single intravitreal administration of VEGF trap eye in patients with DME	A double-masked, randomized, controlled study of the safety, tolerability and biological effect of repeated intravitreal administration of VEGF trap-eye in patients with DME	A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF trap-eye in subjects with DME	A double-masked, randomized, active-controlled, phase 3 study of the efficacy and safety of intravitreal administration of VEGF trap-eye in patients with DME	An open-label phase III study evaluating the safety and tolerability of repeated doses of intravitreal VEGF trap-eye in Japanese subjects with DME	A comparative effectiveness study of intravitreal aflibercept, bevacizumab and ranibizumab for DME
Study design						
Allocation	Non-randomized	Randomized	Randomized	N/A	Randomized	Randomized
Endpoint classification	Safety Study	Safety/Efficacy study	Safety/Efficacy study	Safety/Efficacy study	Safety/Efficacy study	Safety/Efficacy study
Intervention model	Single group assignment	Parallel assignment	Parallel assignment	Single group assignment	Parallel assignment	Parallel assignment
Masking	Open label	Double blind (subject, investigator, outcomes assessor)	Double blind (subject, investigator, outcomes assessor)	Open label	Double blind (subject, investigator, outcomes assessor)	Single blind (subject)
Primary purpose	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Enrollment	5	219	65	466	406	660
Study period	6 wk	52 wk	48 wk	2 yr	52 wk	2 yr
Recruitment status	Completed	Completed	Recruiting	Active, not recruiting	Active, not recruiting	Active, recruiting
Primary outcome measure	To assess the ocular and systemic safety and tolerability of a single IVT injection of VEGF Trap-eye in patients with DME	Change in BCVA	Adverse event collection	Change from baseline of BCVA in ETDRS letter score	Change from baseline of BCVA in ETDRS letter score	Change in visual acuity single blind adjusted for baseline visual acuity
Estimated study completion date	Completed	Completed	2013	2014	2015	2016

BCVA: Best corrected visual acuity; DME: Diabetic macular edema; VEGF: Vascular endothelial growth factor; ETDRS: Early treatment diabetic retinopathy study.

laser group. [+8.5 to +11.4 ETDRS letters *vs* only +2.5 letters in the laser group ( $P \leq 0.0085$  for each aflibercept group *vs* laser) and +127.3 to +194.5  $\mu\text{m}$  *vs* +67.9  $\mu\text{m}$  ( $P = 0.0066$  for each aflibercept group *vs* laser)]. It also showed that aflibercept was well tolerated and its ocular adverse events were consistent with those seen with other intravitreal anti-VEGF agents.

Recently, the DA VINCI study group has also published the results of different doses and dosing regimens of aflibercept with laser photocoagulation in eyes with DME after 52 wk. Assessment of the changes in BCVA and mean changes in CRT at 24 and 52 wk revealed that significant gains in BCVA from baseline, achieved at week 24, were maintained or improved at week 52 in all aflibercept groups. Mean BCVA increases in the aflibercept groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters *vs* -1.3 letters for the laser group ( $P \leq 0.0001$ ).

Mean decrease in CRT in the aflibercept groups at week 52 were -165.4, -227.4, -187.8, and -180.3  $\mu\text{m}$  *vs* -58.4  $\mu\text{m}$  for laser ( $P < 0.0001$ )<sup>[34]</sup>.

At one year, subjects who were treated with aflibercept in the DA VINCI study were doing well. The most frequently reported ocular adverse events associated with aflibercept use were conjunctival hemorrhage (18.9%), increased intraocular pressure (9.7%), eye pain (8.6%), ocular hyperemia (6.3%) and vitreous floaters (5.1%). Serious adverse effects included endophthalmitis (1.1%), uveitis (0.6%), corneal abrasion (0.6%) and retinal tear (0.6%). Systemic adverse events included hypertension (9.7%), cerebral vascular accidents (1.1%), and myocardial infarction (1.1%).

## ONGOING STUDIES

Since the DA VINCI study was not powered sufficiently

to uncover the potential systemic AEs or mortality related to aflibercept, additional phase-III clinical studies of aflibercept have been initiated (Table 2).

### VIVID-Japan

The Japanese Safety Study of VEGF Trap-Eye in DME (VIVID-Japan) is an open-label phase-III study evaluating the safety and tolerability of repeated doses of intravitreal VEGF Trap-Eye (BAY86-5321) in Japanese subjects with DME. Subjects in the aflibercept group will initially receive a loading phase consisting of injections given every 4 wk, followed by an injection every 8 wk. The overall treatment period is 48 wk<sup>[35]</sup>.

### VIVID-DME

VEGF Trap-Eye in Vision Impairment Due to DME (VIVID-DME) was designed to determine the efficacy of intravitreal VEGF Trap-Eye (BAY86-5321) on the BCVA assessed by the ETDRS chart in subjects with DME with central involvement. This multi-central, randomized, double masked, active controlled, phase-III study of the efficacy and safety of repeated doses of intravitreal aflibercept in subjects with DME will assess changes from baseline of BCVA in ETDRS letter score over a 52 wk period in about 375 patients in 91 study locations. The treatment regimens will include 2 arms treated with aflibercept and one with laser therapy according to the ETDRS protocol<sup>[36]</sup>.

### VISTA DME

Study of Intravitreal Administration of VEGF Trap-Eye (BAY86-5321) in Patients with Diabetic Macular Edema (VISTA DME) will assess the efficacy of 2 different dosing regimens of aflibercept compared with laser over the course of 2-year period. VISTA DME is a double-masked, randomized, active-controlled, phase-III study of the efficacy and safety of intravitreal aflibercept in 466 subjects with DME in 52 study locations<sup>[37]</sup>.

### Protocol T

This phase III study sponsored by the Diabetic Retinopathy Clinical Research Network will compare the safety and efficacy of intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg) and ranibizumab (0.5 mg) for DME in 660 patients recruited from different clinical centers in the US. The primary outcome in this study is to evaluate the changes in BCVA at month 12. Protocol T is currently recruiting patients<sup>[38]</sup>.

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