Endolaserless vitrectomy with aflibercept for proliferative diabetic retinopathy-related vitreous hemorrhage (LASER LESS TRIAL):1-Year Results.

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Abstract

Objective: We report the 1-year safety and efficacy results of vitrectomy without endolaser for proliferative diabetic retinopathy (PDR)-related vitreous hemorrhage (VH).

Methods: All eyes received one preoperative and intraoperative IAI (2 mg). The q8week group received postoperative IAI every 4 weeks through week 16 followed by q8week IAI. The q16week group received postoperative IAI every 4 weeks through week 8 followed by q16week IAI. All patients were examined every 4 weeks; PRN IAI for PDR progression or diabetic macular edema (DME) was allowed.

Results: Thirty-one eyes from 40 patients were randomized. Through 52 weeks, endophthalmitis, progression of traction retinal detachment, iris/angle neovascularization and neovascular glaucoma were not observed. The q8week and q16week groups received an average of 8.4 and 5.4 injections, respectively, through 52 weeks. Adverse events at any time through 52 weeks such as worsened visual acuity>30 letters (6 eyes), new rhegmatogenous retinal detachment (1 eye), and recurrent VH (4 eyes) occurred infrequently and were more common in the q16week group. Preoperative average visual acuity (VA) was 37 letters (20/200) for randomized eyes. Endolaserless vitrectomy resulted in statistically significant 52-week visual acuity 33 letter gain to 72 letters (20/40). Visual acuity outcomes favored (not statistically significant) the q8week group where average acuity was 77 letters (20/32) with a 52-week 40 letter gain versus 66 letters (20/50) with a 52-week 24 letter gain in the q16week group.

Conclusion: Endolaserless vitrectomy with aflibercept demonstrates 52-week safety with significant VA improvement.

Keywords: Endolaser, Pars plana vitrectomy, Proliferative diabetic retinopathy, Anti-vascular endothelial growth factor, Vitreous hemorrhage.

Abbreviations: EPDR: Proliferative Diabetic Retinopathy; VH: Vitreous Hemorrhage; DME: Diabetic Macular Edema; BCVA: Best Corrected Visual Acuity; VEGF: Vascular Endothelial Growth Factor; PRP: Pan-Retinal Photocoagulation; PPV: Pars Plana Vitrectomy; IAI: Intravitreal Aflibercept Injection; DRCR: Diabetic Retinopathy Clinical Research; DRVS: Diabetic Retinopathy Vitrectomy Study; HVF: Humphrey Visual Field; OCT: Optical Coherent Tomography; VA: Visual Acuity

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Introduction

Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents is now established as optimal therapy for center-involved diabetic macular edema (DME) [1-4]. Anti-VEGF's ability to reduce retinal neovascularization during DME treatment has led to investigation of anti-VEGF therapy for PDR [5-9] and PDR-related vitreous hemorrhage [10-13]. For over 4 decades, PRP has remained the standard therapy for PDR. However, anti-VEGF therapy has emerged as an alternative therapy for PDR eyes not requiring vitrectomy [5,7-9]. Diabetic Retinopathy Clinical Research (DRCR) Protocol S compared anti-VEGF ranibizumab to PRP for PDR not requiring vitrectomy [5,8].

DRCR Protocol S concluded that their findings supported either anti-VEGF therapy or PRP as viable PDR treatment [8]. The PROTEUS study showed that adding ranibizumab to PRP was more effective than PRP alone in regressing neovascularization in eyes with high-risk PDR [9]. The CLARITY trial further supports anti-VEGF aflibercept therapy in PDR eyes [7]. When PDR was present in eyes being treated for DME in DRCR Protocol T, aflibercept resulted in greater PDR regression rates compared to ranibizumab and Bevacizumab [6].

Given the above information, intravitreal aflibercept injection (IAI) may represent a useful therapy before, during, and after vitrectomy for PDR-related vitreous hemorrhage. We previously reported the short-term 4-month results with endolaserless vitrectomy and aflibercept for eyes with PRP-naïve PDR-related VH [11-13]. Herein, we report 52-week safety and efficacy results for our expanded cohort of 40 eyes.

Materials and Methods

This is a phase I/II, open-label, randomized, prospective, single center interventional study. Eligible subjects were identified and provided with a copy of informed consent. Informed consent documentation and relevant supporting information was submitted and approved by the Institutional Review Board (IRB)/Ethics Committee (EC).

Study population

Adult subjects with Type 1 or Type 2 diabetes mellitus and PDR-related VH requiring vitrectomy. Vitrectomy need was determined by a non-study, standard of care visit prior to the screening study visit. Exclusion criteria are listed in Table 1.

Table 1. *Exclusion criteria.*

Exclusion Criteria	
	A patient who met any of the following criteria were excluded from the study:
	A condition per investigator opinion would preclude participation in the study (unstable medical status, cardiovascular disease, glycemic control, inability to follow up etc.)
	Participation in an investigational trial within 30 days of enrollment
	Known allergy to IAI
	Systemic anti-VEGF or pro-VEGF treatment within 4 months of enrollment
	For women of childbearing age, pregnant or lactating or intending to become pregnant within the next 3 years
	History of PRP or peripheral retinal cryopexy or peripheral retinopexy for any reason in the study eye
	History of vitrectomy in the study eye
	History or evidence for rhegmatogenous retinal detachment in the study eye
	Evidence of traction retinal detachment involving or threatening central macula in the study eye
	Exam evident of external ocular infection (i.e. conjunctivitis, significant blepharitis, chalazion, etc)
	Intravitreal anti-VEGF injection in the study eye<4weeks from enrollment.
	Pregnant or breast-feeding women
	Sexually active men* or women of childbearing potential 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)**
	***Contraception is not required for men with documented vasectomy.**
	****Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child bearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.**

Study design

Only one eye per patient was eligible and was randomly assigned after vitrectomy with equal probability to either a q8week or q16week treatment group. Figure 1 presents the injection and randomization schedule.

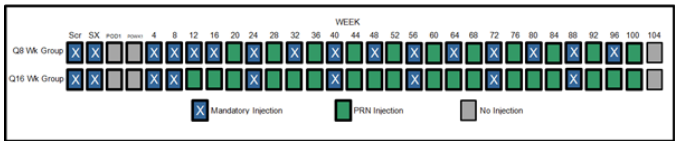

Figure 1. *Aflibercept (2mg) Treatment Schedule: 21 randomized patients with PRP-naïve eyes undergoing vitrectomy for PDR-related vitreous hemorrhage randomized in 1:1 ratio. PRN: pro re nata; Scr: screen; SX: surgery; POD1: post-operative day 1; POWK: post-operative week 1.*

Intraoperative methods and assessment

Eyes underwent 23-gauge PPV. After removal of VH, eyes were intraoperatively evaluated for randomization eligibility. Eyes ineligible for randomization, as determined intraoperative, did not receive intraoperative IAI, but did receive intraoperative endolaser and were followed postoperatively.

Visit schedule

Figure 2 summarizes the visit schedule.

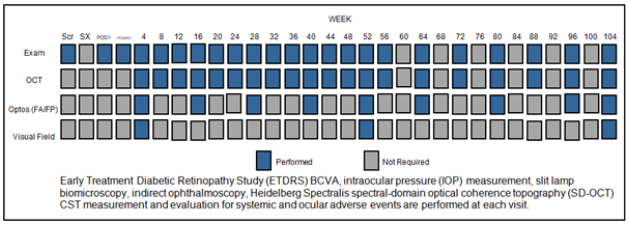

Figure 2. *Visit Schedule. FA: Fluorescein Angiography; FP: Fundus Photography; Scr: screen; SX: Surgery; POD1: post-operative day 1; POWK1: post-operative week 1.*

Post-operative PDR treatment and monitoring

PDR was monitored and assessed for progression by postoperative clinical exam and q12 week standard 7-field fundus photography and Optos wide-field fluorescein angiography/photography. If progression of PDR occurred at a visit where IAI was not mandatory, IAI was required at that visit and in 4 weeks. If regression of the progressed PDR was not evident after 2 consecutive monthly IAI, then PRP could be administered. Criteria for PDR progression and regression are summarized in Table 2.

Table 2. *Criteria for PDR progression and regression.*

Criteria for PDR Progression and Regression	
Progression of PDR was defined as any of the following:	
	Increase or new neovascularization of the retina, optic disc or iris/angle as determined by clinical exam, fundus photography or fluorescein angiography compared to previous postoperative visits/photos/ angiography
	Progression of or new PDR-related traction retinal detachment as determined by clinical exam, fundus photography or fluorescein angiography compared to previous postoperative visits/photos/ angiography
	Increase or new PDR-related vitreous hemorrhage as determined by clinical exam, fundus photography or fluorescein angiography compared to previous postoperative visits/photos/angiography (Persistence of vitreous hemorrhage in the early (<8wks postoperatively) postoperative period was not be considered progression unless there was an increase or persisted without clearing past 8 weeks postoperatively)
Regression from previously progressed PDR was defined as any of the following:	
	Decrease or resolution of the previously identified increase or new neovascularization of the retina, optic disc or iris/angle as determined by clinical exam, fundus photography or fluorescein angiography.
	Decrease or resolution of previously identified progression of or new PDR-related traction retinal detachment as determined by clinical exam, fundus photography or fluorescein angiography.
	Decrease or resolution of previously identified increase or new PDR-related vitreous hemorrhage as determined by clinical exam, fundus photography or fluorescein angiography

DME treatment and monitoring

Eyes with clinical and optical coherent tomography (OCT) DME in the q8week group were to receive appropriate IAI per label as part of the mandatory schedule through 16 weeks. Starting at week 12 and week 20 in the q16 and q8week groups, respectively, eyes were eligible to receive additional 2mg IAI (monthly) for the treatment of DME (Table 3).

Table 3. *Criteria for additional monthly IAI for DME.*

Criteria for Additional Monthly IAI for DME	
	Eyes were eligible for additional IAI for DME at monthly visits in between the q8week or q16week IAI visits if all the following criteria are met.
	Loss of>5 letters best previously recorded VA and loss of acuity felt to be secondary to DME and not from other cause (ie: cataract, epiretinal membrane, etc)
	Any increase in OCT CSF from best previously recorded OCT CSF and any evidence of subretinal or intraretinal fluid
	Investigator feels patient would benefit from additional IAI therapy

Outcome Measurements

Primary outcomes

Primary safety outcomes are summarized in Table 4.

Table 4. *Primary safety outcomes.*

Primary Safety Outcomes	
The primary objective of the study is ocular and systemic safety evaluation at any time point through 52 weeks for adverse events defined as:	
	Worsened acuity>30 letters
	Rhegmatogenous or tractional retinal detachment
	New or increased vitreous hemorrhage
	Cataract progression or surgery
	Need for additional vitrectomy or scleral buckle
	Need for PRP
	Development of new DME after OCT documentation of absence of DME
	Systemic thromboembolic events
	Development of new DME after OCT documentation of absence of DME
	Systemic serious adverse events
	Deaths
	Proportion of eyes with progression of or new traction retinal detachment secondary to PDR at any time point through week 52
	Proportion of eyes developing new iris or angle neovascularization or neovascular glaucoma any time point through week 52
	Increase or new neovascularization of the retina, optic disc or iris/angle as determined by clinical exam, fundus photography or fluorescein angiography compared to previous postoperative visits/photos/angiography

Secondary outcomes

Secondary outcomes are summarized in Table 5. Qualitative angiographic outcomes were evaluated based on size and leakage intensity of hyper fluorescence. Qualitative photographic outcomes were based on photographic DME/exudate size and thickness.

Table 5. *Secondary outcomes.*

Secondary Outcomes	
The secondary objectives of the study are to evaluate additional efficacy and safety outcomes listed:	
	Vision Outcomes
	•Mean change in BCVA letter score over time through week 52 and 104 and 152
	•Mean BCVA letter score over time through week 52 and 104 and 152
	Anatomic Outcome(s):
	•Proportion of eyes with progression of PDR at any time point as defined above through 52 and 104 and 152 weeks
	•Mean OCT CSF thickness over time through week 52 and 104 and 152
	•Proportion of eyes with absence of Optos wide-field fluorescein angiographic macular leakage at week 52 and 104 and 152
	•Proportion of eyes with absence of active neovascularization by Optos wide field fluorescein angiography and 7 standard field photography at week 52 and 104 and 152
	•Proportion of eyes with unchanged, worsened, or improved fluorescein angiographic macular leakage from baseline angiograms at week 52 and 104 and 152
	•Proportion of eyes with OCT CSF thickness <300um at week 52 and 104 and 152
	•Proportion of eyes with unchanged, worsened, or improved fluorescein angiographic neovascularization from baseline angiograms at week 52 and 104 and 152
	•Proportion of eyes with unchanged, worsened, or improved fundus photographic DME appearance from baseline photographs at week 52 and 104 and 152
	Functional Outcome(s):
	•Mean cumulative score and change for the combined 30-2 and 60-4 HVF test from week 4 to week 52 and to week 104 and 152
	Treatment Outcome(s):
	•Proportion of eye requiring additional IAI other than mandatory injections through week 52 and 104 and 152
	•Proportion of eye with progression of PDR requiring rescue PRP standard of care at any time point through week 52 and 104 and 152
	•Proportion of q8week eyes meeting stability criteria at week 104
	Other Outcome(s):
	•Proportion of eyes requiring PRP or retinopexy at any time point through week 52 and 104 and 152
	•Proportion of eyes requiring additional vitrectomy at any time point through week 52 and 104 and 152
	•Proportion of enrolled eyes requiring intraoperative endolaser in a PRP pattern at the time of initial vitrectomy.

Visual field outcomes were evaluated by the mean cumulative score and change for the combined 30-2 and 60-4 Humphrey visual field (HVF) decibel thresholds from week 4 to week 52.

Results/Observations

Study participants

Forty eyes from 40 subjects were enrolled. Baseline demographics are presented in Table 6. All eyes received preoperative IAI at enrollment. Two intraoperative retinal tears, in two eyes, were treated with intraoperative retinal cryopexy. Five of the 31 randomized eyes required membrane peel for non-macular traction. Average surgical time was 21 minutes (range: 12-47 minutes) for randomized eyes. Twenty-five of 31 (81%) randomized subjects completed their 52-week follow-up visit. Figure 3 summarizes patient randomization and retention.

Table 6. *Baseline Demographics for 31 randomized eyes. One subject declined vitrectomy after enrollment and receipt of pre-operative IAI. This subject continues follow-up for safety as a nonrandomized eye. One subject was unable to undergo vitrectomy after enrollment and receipt of pre-operative IAI due to accelerated hypertension at time of surgery. This subject has been lost to follow-up since the decision to not undergo surgery. Thirty-eight of 40 enrolled eyes underwent vitrectomy surgery. Seven of those 39 eyes were not randomized due to intraoperative evidence of previous peripheral retinal ablation (2 eyes), traction retinal detachment involving the macula (2 eyes), significant nasal fibrovascular proliferation and noncentral nonmacular traction retinal detachment (1 eye), cataracts and retrolental hemorrhage (1 eye), and intraoperative tears (1 eye). These seven non-randomized eyes received intraoperative endolaser and did not receive intraoperative IAI and continue follow-up for safety as nonrandomized eyes.*

	Q8 wk group	Q16 wk group	Overall (40 enrolled)
PPV completed	14	17	38
Randomized	14	17	31 (9 not randomized)
Gender	10 males, 4 females	8 males, 9 females	18 males, 13 females

Diabetes	13 Type II, 1 Type I	14 Type II, 3 Type I	27 Type II, 4 Type I
Insulin	4 Insulin-Independent,	7 Insulin-Independent,	11 Insulin-Independent,
	10 Insulin-Dependent	10 Insulin-Dependent	20 Insulin-Dependent
Race	7 White, 6 AA, 1 Asian	3 White, 13 AA, 1 Asian	10 White, 19 AA, 2 Asian
Age	Avg: 56 (range: 41-74)	Avg: 55 (range: 26-77)	Avg: 56 (range: 26-77)
Lens Status	10 Phakic, 4 Pseudophakic	15 Phakic, 2 Pseudophakic	25 Phakic, 6 Pseudophakic
# Previous Anti-VEGF Injections Prior to Enrollment	Avg: 1.4 (range: 0-8)	Avg: 1.6 (range: 0-22)	Avg: 1.5 (range: 0-22)
*AA: African American; PPV: Pars Plana Vitrectomy; wk: week			

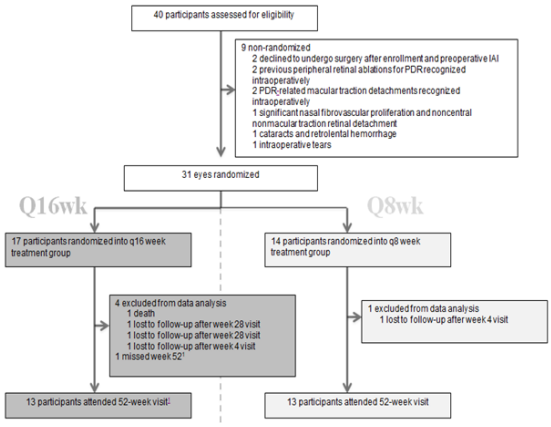

Figure 3. *Participant randomization and retention. Last observation carried forward (LOCF) from week 48 was used for this participant for week 52 analysis.*

Primary safety outcomes

Adverse primary safety outcomes are summarized in Table 7. All adverse events are summarized in Table 8. Treatment schedules for two subjects experiencing recurrent vitreous hemorrhages are presented in Figures 4 and 5.

Table 7. *Primary safety outcomes results through 52 weeks.*

Adverse Events at any time through 52 Weeks	q8week n=14	q16week n=17	Non-Randomized n=9	Overall-Randomized n=31
Worsened Acuity>30 letters	2/14	4/17	0/9	6/31
New Rhegmatogenous Retinal Detachment	0/14	1/17*	0/9	1/31
New or Progressed Tractional Retinal Detachment	0/14	0/17	1/9	0/31
Endophthalmitis	0/14	0/17	0/9	0/31
New or Increased Vitreous Hemorrhage	1/14	3/17	0/9	4/31
Cataract Progression or Surgery	1/14	1/17	1/9	2/31
New Iris/Angle Neovascularization or Neovascular Glaucoma	0/14	0/17	0/9	0/31
Need for Additional Vitrectomy or Scleral Buckle	0/14	0/17	1/9	0/31
Development of New DME after OCT documentation of absence of DME	1/14	0/17	0/9	1/31
Systemic Thromboembolic events	0/14	2/17 (Acute cardiac arrest, TIA)	1/9 (non-ST elevated myocardial infarction)	2/31
Systemic Serious Adverse Events	0/14	4/17 (Severe peripheral edema/acute cardiac arrest, DKA, TIA, Low Hemoglobin Transfusion)	1/9 (non-ST elevated myocardial infarction)	4/31
Need for Additional Panretinal Photocoagulation	0/14	0/17*	0/9	0/31
Deaths	0/14	1/17	0/9	1/31
DKA: Diabetic ketoacidosis, TIA: Transient Ischemic Attack *Retinal Detachment identified at week 52 visit and repair with PPV performed after week 52				

Table 8. *Adverse events.*

Ocular	# of Study Eyes	# of Non-study Eyes		# of Study Eyes	# of Non-study Eyes
Old and New Intraoperative Retinal Tears	2	0	Ocular Pain	3	0
Vitreous Hemorrhage	4	6	Retinal Tear	2	5
Increased Posterior Capsule Opacification	3	1	Local RD SRF SE OD	2	1
YAG Laser	1	0	Blurry Vision	1	0
Neovascularization of Disc	0	2	Macular Hole-likely preexisting	0	1
Cataract Extraction	2	3	Cholesterol Embolism-likely preexisting	1	2
Worsening of Cataracts	2	0	Local Endolaser<200	1	0
Tractional Retinal Detachment	1	2	Intraoperative Peripheral Tear	1	0
Subconjunctival Hemorrhage	0	2	Conjunctivitis	2	1
Posterior Subcapsular Cataract	1	1	Vitreomacular Traction with Foveal Edema	0	1
Worsening Posterior Subcapsular Cataract	0	1	Epiretinal Membrane	1	0
Posterior Vitreous Detachment	0	1	Elevated Intraocular Pressure	1	1
Systemic AE	**# of Patients**	**Systemic AE**	**# of Patients**	**Systemic AE**	**# of Patients**
Severe Peripheral Edema (Anasarca)	1	Ankle Edema	1	Dizziness	1
Non-ST elevated Myocardial Infarction	1	Tooth Removal	1	Depression	1
Worsening Hypertension	5	Hypotension	1	Anemia	1
Sprained Wrist	1	Bruised Ribs	1	Syncope	1
Kidney Stone Removal	1	Upper Respiratory Infection	1	Right Arm Graft Sx S/P Dialysis	1
Acute Cardiac Arrest	1	Kidney Stones	1	Seasonal Allergies	3
Diabetic Ketoacidosis	1	Intestinal Infection	1	Sinus Infection	1
Influenza	4	Head Injury	1	Bronchitis	1

Common Cold	2	Back Injury	2	Urinary Tract Infection	1
Hip Pain	2	Transient Ischemic Attack	2	Stomach Virus	1
Chronic Headaches	1	Acute Exacerbation of COPD Symptoms	1	Peritoneal Dialysis catheter surgery	1
Broken Toe	1	Bruised Ribs	1		

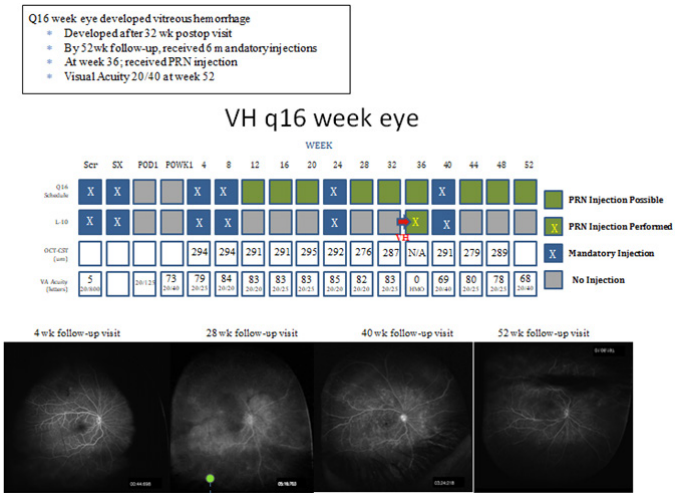

Figure 4. *Vitreous hemorrhage case presentation, VH: Vitreous Hemorrhage.*

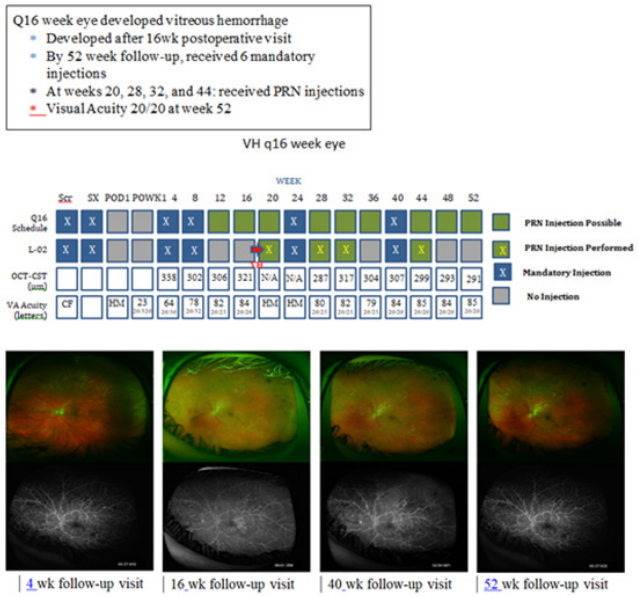

Figure 5. *Vitreous hemorrhage case presentation; VH: Vitreous Hemorrhage.*

Injection treatment requirement and compliance

An average of 8.4 (range: 2 to 10) and 5.4 (range: 2 to 9) total injections though 52 weeks were administered to the q8week and q16week treatment groups, respectively (Table 9).

Table 9. *Follow-up and injection compliance.*

Aflibercept Injection Schedules/Compliance	Q8 Group (n=14)	Q16 Group (n=17)
4 weeks	14/14 eyes	16/17 eyes *1 missed injection- High BP
8 weeks	13/14 eyes *1 missed visit	14/17 eyes *3 missed visit
12 weeks	12/14 eyes *1 missed visit *1 missed injection	1/17 eyes *3 missed visits PRN inj. for PDR: 0 eyes PRN inj. for DME: 1 eye
16 weeks	13/14 eyes *1 missed visit	3/17 eyes *3 missed visits
		PRN for PDR: 2 eyes PRN for DME: 1 eye
20 weeks	0/14 *1 missed visit PRN for PDR: 0 eyes PRN for DME: 0 eyes	2/17 eyes *3 missed visits PRN for PDR: 2 eyes PRN for DME: 0 eyes
24 weeks	0/14 eyes *1 missed visit	14/17 eyes *3 missed visit
28 weeks	0/14 eyes *1 missed visit PRN for PDR: 0 eyes PRN for DME: 0 eyes	3/17 eyes PRN for PDR: 2 eyes PRN for DME: 1 eye
32 weeks	0/14 eyes *1 missed visit	2/17 eyes *3 missed visit PRN for PDR: 1 eye PRN for DME: 1 eye
36 weeks	1/14 eyes *3 missed visits PRN for PDR: 0 eyes PRN for DME: 1 eye	2/17 eyes *4 missed visits PRN for PDR: 1 eye PRN for DME: 1 eye
40 weeks	0/14 eyes *2 missed visit	13/17 eyes *1 deceased *3 missed visit
44 weeks	2/14 eyes *2 missed visit PRN for PDR: 2 eyes PRN for DME: 0 eyes	2/17 eyes *1 deceased *3 missed visit PRN for PDR: 2 eyes PRN for DME: 0 eyes
48 weeks	13/14 eyes *1 missed visit	0/17 eyes *1 deceased *3 missed visit PRN for PDR: 0 eyes PRN for DME: 0 eyes
52 weeks	13/14 eyes *1 missed visit	2/17 eyes *1 deceased *3 missed visits PRN for PDR: 1 eye PRN for DME: 1 eye

*PRN: pro re nata; Shaded: mandatory scheduled injections for PDR (Numerator: #of eyes received mandatory scheduled injections for PDR, Denominator: # of eyes scheduled for mandatory scheduled injections for PDR; Non-shaded: Non-mandatory scheduled injections/PRN injections administered for PDR progression or DME (Numerator: #of Eyes received PRN injection for PDR progression or DME, Denominator: # of eyes scheduled for evaluation by PI for PRN injection)

Visual acuity outcomes

Endolaserless vitrectomy with IAI resulted in statistically significant VA gain for all eyes and in both groups (Table 10, Figure 6). Baseline preoperative VA letter score for 31 randomized eyes was 37 letters (20/200) (range: 0 to 84 letters). For 26 randomized eyes in both groups with 52-week follow-up, baseline preoperative VA letter score was 40 letters (20/160) (range: 0 to 84 letters). At 52 weeks, the average best corrected visual acuity (BCVA) score improved to 72 letters (20/40) with an average change in BCVA of +33 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline (range: -10 to 90 letters) ($p<0.00004$; one tailed t-test). For randomized eyes in the q8week group with 52-week follow-up, average BCVA improved to 77 letters (20/32) with an average letter gain of +40 ETDRS letters (range: -10 to 90 letters) ($p<0.0009$; one-tailed t-test). For randomized eyes in the q16week group with 52-

week follow-up, average BCVA improved to 66 letters (20/50) with an average letter gain of +24 letters (range: -6 to 85 letters) (p<0.0097; one-tailed t-test). Baseline letter score did not show a statistically significant difference between the two groups (35 letters q8week and 42 letters q16week) (p<0.882; two-tailed t-test). Letter score change from baseline favored the q8week group (40 letter gain q8week versus 24 letter gain q16week) but this was not statistically significant (p<0.480; two-tailed t-test).

Table 10. *Visual acuity change from baseline.*

	Q8week Treatment group (n=14)	Q16week Treatment group (n=17)	Overall
Preoperative BCVA	32 letters (range: 0 to 77) n=14	38 letters (range: 0 to 84) n=17	37 letters (range: 0 to 84) n=31
4-week visual gain	37 letters (range: 2 to 84) n=14	24 letters (range: -13 to 74) n=17	30 letters (range: -13 to 84) n=31
8-week visual gain	36 letters (range: -1 to 82) n=13 1 missed visit	27 letters (range: -11 to 79) n=14 3 missed visit	31 letters (range: -11 to 82) n=27 4 missed visits
12-week visual gain	40 letters (range: 6 to 86) n=13 1 missed visit	26 letters (range: -2 to 82) n=14 3 missed visits	33 letters (range: -2 to 86) n=27 4 missed visits
16-week visual gain	40 letters (range: 3 to 84) n=13 1 missed visit	26 letters (range: -17 to 84) n=14 3 missed visits	33 letters (range: -17 to 84) n=27 4 missed visits
20-week visual gain	41 letters (range: 1 to 89) n=13 1 missed visit	26 letters (range: -16 to 78) n=14 3 missed visits	29 letters (range: -16 to 89) n=27 4 missed visits
24-week visual gain	38 letters (range: -10 to 84) n=13 1 missed visit	19 letters (range: -8 to 80) n=14 3 missed visits	28 letters (range: -10 to 84) n=27 4 missed visits
28-week visual gain	41 letters (range: 0 to 89) n=13 1 missed visit	23 letters (range: -9 to 80) n=15 2 missed visits	31 letters (range: -9 to 89) n=28 3 missed visit
32-week visual gain	40 letters (range: -5 to 90) n=12 2 missed visits	27 letters (range: -10 to 82) n=14 3 missed visits	33 letters (range: -10 to 90) n=26 5 missed visits
36-week visual gain	35 letters (range: -6 to 90) n=11 3 missed visits	21 letters (range: -13 to 79) n=14 3 missed visits	27 letters (range: -13 to 90) n=25 6 missed visits
40-week visual gain	32 letters (range: -7 to 90) n=12 2 missed visits	27 letters (range: -12 to 84) n=13 4 missed visits	29 letters (range: -12 to 90) n=15 6 missed visits
44-week visual gain	27 letters (range: -68 to 88) n=12 2 missed visits *1 eye with -68 letter loss due to VH	29 letters (range: -10 to 85) n=13 4 missed visits	28 letters (range: -68 to 88) n=15 6 missed visits
48-week visual gain	32 letters (range: -5 to 93) n=12 2 missed visits	28 letters (range: -15 to 84) n=13 4 missed visits	30 letters (range: -15 to 93) n=25 5 missed visits
52-week visual gain	40 letters (range: -10 to 90) n=12 2 missed visits *1 eye with -10 letter loss due to DME	24 letters (range: -8 to 85) n=13 4 missed visits	33 letters (range: -10 to 90) n=26 5 missed visits

*BCVA: Best Corrected Visual Acuity; VH: Vitreous Hemorrhage; DME: Diabetic Macular Edema

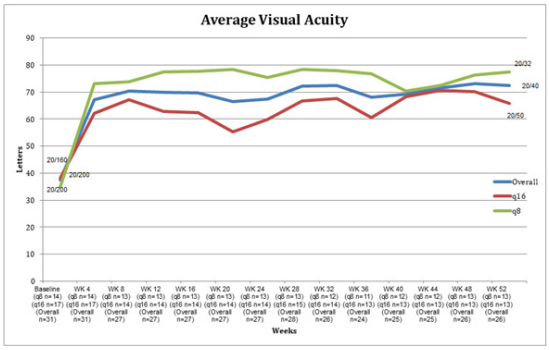

Figure 6. *Average visual acuity.*

OCT Outcomes

Baseline OCT was performed at 4 weeks postoperatively in 31 randomized eyes with no statistically significant difference between the two groups but thinner in the q16week group (336 um q8week group and 282 um q16week group) (p<0.408; two-tailed t-test). Endolaserless vitrectomy with IAI resulted in statistically significant OCT thinning from week 4 to week 52 for all eyes in the q8week but not in the q16week group (Table 11, Figure 7). For 26 randomized eyes at 52-week follow-up, average OCT central subfoveal thickness (CST) was 264 um (range: 147 to 338 um), which displayed an average thinning of 33 um from the baseline OCT 4-week postoperative visit (p<0.000014; one-tailed t-test). For randomized eyes in the q8week group with 52-week follow-up, average 52 week OCT CST was 270 um with an average thinning of 53 um from baseline (p<0.004; one-tailed t-test). For randomized eyes in the q16week group with 52 week follow-up, average 52 week OCT CST was 255 um with an average thinning of 12 um from baseline (p<0.165; one-tailed t-test). Fifty-two week OCT thickness change (53 um thinning q8week group and 12 um thinning q16week group) from baseline favored the q8week group (not statistically significant) (p<0.312; two-tailed t-test)

Table 11. *Average OCT values through 52 weeks post-operatively.*

	Q8 group	Q16 group (N=17)	Overall (31 randomized)
4-week post-op (baseline)	336 um (range: 242 to 476) *7/14 eyes>300 um	282 um (range: 132 to 468) *4/17 eyes>300 um	311 um (range: 132 to 476) *11/31 eyes>300 um
8-week post-op	321 um (range: 236 to 504) *5/13 eyes>300 um *1 missed visit	265 um (range: 124 to 318) *2/14 eyes>300 um *3 missed visits	265 um (range: 124 to 318) *2/14 eyes>300 um *3 missed visits
12-week post-op	293 um (range: 230 to 358) *5/13 eyes>300 um *1 missed visit	257 um (range: 136 to 306) *1/14 eyes>300 um *3 missed visits	275 um (range: 136 to 358) *6/27 eyes>300 um *4 total missed visits
16-week post-op	285 um (range: 225 to 333) *4/13 eyes>300 um *1 missed visit	259um (range: 148 to 337) *2/14 eyes>300 um *3 missed visits	272 um (range: 148 to 333) *6/27 eyes>300 um *4 total missed visits
20-week post-op	286 um (range: 226 to 327) *5/13 eyes>300 um *1 missed visit	256 um (range: 123 to 298) *0/14 eyes>300 um *3 missed visits	272 um (range: 123 to 320) *5/27 eyes>300 um *4 total missed visits

24-week post-op	363um (range: 232 to 548) *7/13 eyes>300 um *1 missed visit	281um (range: 122 to 435) *2/14 eyes>300 um *3 missed visit	322 um (range: 122 to 548) *9/27 eyes>300 um *4 total missed visits
28-week post-op	281 um (range: 231 to 318) *3/13 eyes>300 um *1 missed visit	300 um (range: 136 to 653) *2/14 eyes>300 um *3 missed visits	292 um (range: 136 to 653) *5/27 eyes>300 um *4 total missed visits
32-week post-op	324 um (range: 227 to 612) *4/12 eyes>300 um *2 missed visit	260um (range: 116 to 318) *3/14 eyes>300 um *3 missed visits	290 um (range: 116 to 612) *7/26 eyes>300 um *5 total missed visits
36-week post-op	286 um (range: 224 to 320) *3/11 eyes>300 um *3 missed visit	258 um (range: 160 to 317) *2/13 eyes>300 um *1 no view *4 missed visits	271 um (range: 160 to 320) *5/24 eyes>300 um *1 no view *7 total missed visits
40-week post-op	325 um (range: 230 to 624) *3/13 eyes>300 um *2 missed visit	264 um (range: 110 to 317) *3/13 eyes>300 um *3 missed visits *1 deceased	295 um (range: 110 to 624) *6/26 eyes>300 um *6 total missed visits
44-week post-op	281 um (range: 235 to 321) *2/13 eyes>300 um *1 missed visit	263 um (range: 140 to 303) *2/13 eyes>300 um *4 missed visit *1 deceased	272 um (range: 140 to 321) *4/26 eyes>300 um *6 total missed visits
48-week post-op	321 um (range: 236 to 574) *3/13 eyes>300 um *1 missed visit	263 um (range: 119 to 306) *2/13 eyes>300 um *3 missed visits *1 deceased	292 um (range: 119 to 574) *5/26 eyes>300 um *5 total missed visits
52-week post-op	270 um (range: 222 to 338) *2/13 eyes>300 um *1 missed visit	255 um (range: 147 to 319) *2/12 eyes>300 um *4 missed visits *1 deceased *1 no view	263 um (range: 147 to 338) *4/25 eyes>300 um *6 total missed visits *1 no view

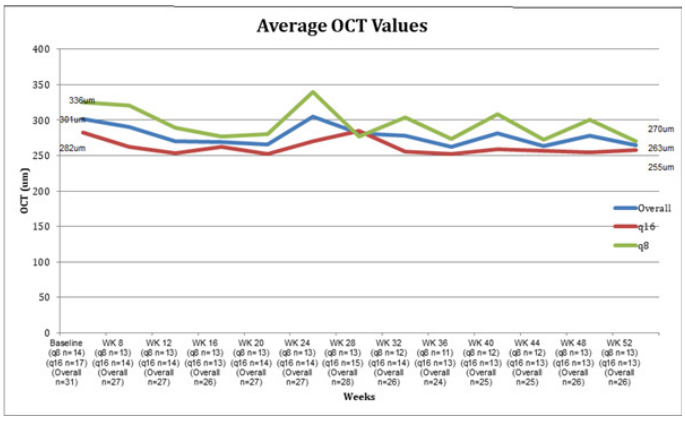

Figure 7. *Average OCT values.*

Eight of 31 randomized eyes (5 in q8week group and 3 in q16week group) demonstrated DME intraoperatively. At 4 weeks and 52 weeks postoperatively, OCT CST>300 um was observed in 11 of 31 randomized eyes (7 in q8week group and 4 in q16week group) and 4 of 25 randomized eyes (2 in q8week group and 2 in q16week group), respectively. Clinical DME at 52 weeks postoperatively was observed in 3 of 25 eyes (1 in the q8week group and 2 in the q16week group) (Table 12).

Table 12. *Clinical DME evaluation and incidence.*

	Q8 group (n=14)	Q16 group (n=17)	Overall (31 randomized)
Evaluable Pre-operative DME	4/14 eyes *4 unable to evaluate	4/14 eyes *4 unable to evaluate	8/31 *7 total unable to evaluate due to vitreous hemorrhage
Intraoperative DME	5/14 eyes	2/17 eyes	7/31 eyes
4 weeks post-op	7/14 eyes	7/17 eyes	14/31 eyes
8 weeks post-op	5/13 eyes *1 missed visit	4/14 eyes *3 missed visit	9/27 eyes *4 total missed visits
12 weeks post-op	5/13 eyes *1 missed visit	5/13 eyes *1 missed visit	9/27 eyes *4 total missed visits
16 weeks post-op	4/13 eyes *1 missed visit	5/14 eyes *3 missed visits	9/27 eyes *4 total missed visits
20 weeks post-op	4/13 eyes *1 missed visit	4/14 eyes *3 missed visits *1 unable to evaluate	8/27 eyes *4 total missed visits *1 unable to evaluate due to recurrent vitreous hemorrhage
24 weeks post-op	4/13 eyes *I missed visits	3/14 eyes *3 missed visits *1 unable to evaluate	7/27 eyes *4 total missed visits *1 unable to evaluate due to recurrent vitreous hemorrhage
28 weeks post-op	3/13 eyes *1 missed visit	2/14 eyes *3 missed visits	4/27 eyes *4 total missed visit
32 weeks post-op	3/12 eyes *2 missed visit	4/14 eyes *3 missed visits	6/26 eyes *5 total missed visits
36 weeks post-op	2/11 eyes *3 missed visits	2/13 eyes *4 missed visits *1 unable to valuate	4/24 eyes *7 total missed visits *1 unable to evaluate due to recurrent vitreous hemorrhage
40 weeks post-op	1/12 eyes *2 missed visits	1/13 eyes *3 missed visit *1 deceased	2/25 eyes *6 total missed visits
44 weeks post-op	1/12 eyes *1 missed visit	0/13 eyes *4 missed visit *1 deceased	1/25 eyes *6 total missed visits
48 weeks post-op	2/13 eyes *1 missed visits	0/13 eyes *3 missed visit *1 deceased	2/26 eyes *5 total missed visits
52 weeks post-op	1/13 eyes *1 missed visit	2/12 *4 missed visits *1 deceased *1 unable to evaluate	3/25 eyes *6 total missed visits *1 unable to evaluate due to retinal detachment

Fundus Photographic (FP) and Wide-Field Fluorescein angiographic (FA) grading

Fundus photographic and wide-field fluorescein angiographic grading is presented in Table 13.

Table 13. *Fundus photographic and wide-field fluorescein angiographic grading.*

Progression of PDR at any time point through 52 Weeks						
	Q8week (n=14)		**Q16week (n=17)**		**Overall (n=31)**	
Yes	3	21%	5	29%	8	26%
No	10	71%	8	47%	18	58%
Lost to Follow-up	1	6%	4	24%	5	16%
FA Neovascularization at Week 52						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Absence	10	71%	6	35%	16	52%
Presence	3	21%	7	41%	10	48%
Lost to Follow-up	1	6%	4	24%	5	16%
FA Neovascularization compared to Baseline at Week 52						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Improved	6	43%	1	6%	7	23%
Worsened	0	0%	2	12%	2	6%
Unchanged	7	50%	10	59%	17	52%
Lost to Follow-up	1	6%	4	24%	5	16%
FA Macular Leakage compared to Baseline at Week 52						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Improved	10	71%	7	41%	17	52%
Worsened	1	7%	2	12%	3	10%
Unchanged	2	14%	4	24%	6	19%
Lost to Follow-up	1	7%	4	24%	5	16%
Fundus Photo DME Appearance Compared to Baseline						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Improved	2	14%	2	12%	6	19%
Worsened	1	7%	2	12%	3	10%
Unchanged	9	64%	7	41%	16	52%
Lost to Follow-up	1	7%	4	24%	5	16%
Indeterminate	1	7%	2	12%	3	10%
FA Macular Leakage Appearance at Week 52						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Absence	2	14%	4	24%	6	19%
Presence	11	79%	9	53%	20	65%
Lost to Follow-up	1	7%	4	24%	5	16%
OCT CSF<300						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Yes	11	79%	8	47%	19	61%
No	2	14%	4	24%	6	19%
Lost to Follow-up	1	7%	4	24%	5	16%
Unable to Obtain	0	0%	1	6%	1	2%
Requiring additional IAI other than Mandatory Injections						
	Q8week (n=14)		Q16week (n=17)		Overall (n=31)	
Yes	3	21%	7	41%	10	48%
No	11	79%	10	59%	21	52%

Humphrey visual field outcomes

Sample size for HVF score analysis was a limitation in our analysis. Also, due to equipment malfunction, not all patients were able to undergo visual field testing at their week 52 visit (Table 14). Baseline mean total HVF point score combining 30-2 and 60-4 was 2573 dB [SD, 658 dB] at week 4 for 28 randomized eyes. For the 21 total randomized eyes from both groups with both baseline and 52-week HVF testing, average total score was 2269 dB [SD, 649 dB] at week 52 with an average change of -440 dB ($p<0.007$; one tailed t-test). Additional secondary treatment outcomes are summarized in Table 15.

Table 14. *Humphrey visual field.*

Cumulative HVF Score at Baseline (dB) Q8 Group at Week 4			
	HVF 30-2 N=11	HVF 60-4 N=11	HVF 30-2+HVF 60-4
Median Score dB (25th, 75th percentile)	1897 (1808, 2089)	995 (845, 1193)	2808 (2653, 3205)
Cumulative HVF Score at Baseline (dB) Q8 Group at Week 52			
	HVF 30-2 N=11	HVF 60-4 N=11	HVF 30-2+HVF 60-4
Median Score dB (25th, 75th percentile)	1782 (1556,1893)	627 (416, 908)	2457 (1977, 2748)
Mean ± SD	1671 ± 458	647 ± 307	2318 ± 551
Cumulative HVF Score at Baseline (dB) Q16 Group at Week 4			
	HVF 30-2 N=10	HVF 60-4 N=10	HVF 30-2+HVF 60-4
Median Score dB (25th, 75th percentile)	1884 (1496, 2169)	832 (480, 938)	2756 (1872, 3081)
Mean ± SD	1723 ± 570	810 ± 488	2534 ± 750
Cumulative HVF Score at Baseline (dB) Q16 Group at Week 52			
	HVF 30-2 N=10	HVF 60-4 N=10	HVF 30-2+HVF 60-4
Median Score dB (25th, 75th percentile)	1562 (1286, 1718)	573 (467, 943)	2115 (1777, 2569)
Mean ± SD	1526 ± 658	690 ± 390	2216 ± 765
Cumulative HVF Score at Baseline (dB) Overall at Week 4			
	HVF 30-2 N=21	HVF 60-4 N=21	HVF 30-2+HVF 60-4
Median Score dB (25th, 75th percentile)	1897 (1728, 2173)	886 (643, 1168)	2776 (2552, 3135)

Mean ± SD	1829 ± 432	881 ± 424	2710 ± 605
Cumulative HVF Score at Baseline (dB) Overall at Week 52			
	HVF 30-2 N=21	HVF 60-4 N=21	HVF 30-2+HVF 60-4
Median Score dB (25th, 75th percentile)	1641 (1461,1886)	626 (455, 942)	2415 (1734, 2704)
Mean ± SD	1601 ± 552	668 ± 341	2269 ± 649

Table 15. *Additional secondary outcomes.*

Secondary Outcomes through 52 Weeks	**Q8 Group**	**Q16 Group**	**Overall**
Functional Outcome(s):	n=11	n=10	n=21
Mean cumulative score and change for the combined 30-2 and 60-4 HVF test	Week 4: 2869	Week 4: 2534	Week 4: 2710
	Week 52: 2318	Week 52: 2216	Week 52: 2269
	Change: -551	Change: -318	Change: -441
Treatment Outcome(s):	n=14	n=17	n=31
Eyes requiring additional IAI other than mandatory injections	3/14	7/17	10/31
Eyes with progression of PDR requiring rescue PRP standard of care at any time point	0/14	0/17*	0/31
Other Outcome(s):	n=14	n=17	n=40 (9 non randomized eyes)
Eyes requiring PRP or retinopexy at any time point	0/14	0/17*	0/31
Eyes requiring additional vitrectomy at any time point	0/14	0/17	0/31
Eyes requiring intraoperative endolaser in a PRP pattern at the time of initial vitrectomy.	0/14	0/17	8/40 enrolled eyes required PRP due to randomization ineligibility evaluated intraoperatively.

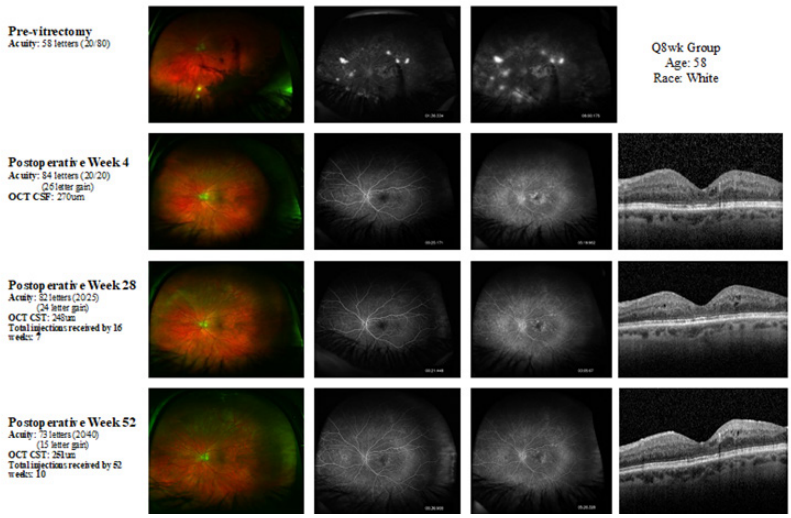

Figure 8. *Case presentation.*

Non-randomized eyes Demographics and outcomes for the 9 non-randomized eyes are summarized in Table 16.

Table 16. *Baseline demographics, visual acuity, and 52-week outcomes for non-randomized subjects.*

Subject	L-03	L-20	L-22	L-26	L-27	L-33	L-37	L-39	L-40
Gender	Male	Male	Female	Male	Female	Female	Male	Female	Male
Diabetes	Type II	Type II	Type II	Type II	Type II	Type II	Type I	Type II	Type II
Race	African American	African American	African American	African American	African American	African American	African American	White	African American
Age	58	41	46	65	68	38	29	59	42
Lens Status	Pseudo	Phakic	Phakic	Phakic	Phakic	Phakic	Phakic	Phakic	Phakic
# Previous Injections Prior to Enrollment	9 Avastin	0	0	0	0	1 Avastin	0	0	0
# IAI Aflibercept After Enrollment	7	1 (at screen)	1 (at screen)	1 (at screen)	1 (at screen)	1 (at screen)	1 (at screen)	2 (both pre-PPV/EL)	1 (at screen)

Reason for Nonrandomization	Elected to not undergo PPV	Previous PRP found intraoperatively	PDR-related macular traction detachment found intraoperatively	Elected to not undergo PPV due to accelerated hypertension-failed to return for surgery	Previous PRP found intraoperatively	PDR-related macular traction detachment found intraoperatively	Significant nasal Fibrovasuclar proliferation and noncentral nonmacular TRD	cataracts and retrolental heme	Intraoperative tears
VA Outcomes									
Baseline (screen)	53 (20/100)	69 (20/40)	28 (20/250)	65 (20/50)	0	0	0	0	0
Week 52	75 (20/32)	Lost to Follow-up	67 (20/50)	Lost to Follow-up	Lost to Follow-up	68	Lost to Follow-up	Expected in March 2019	Expected in May 2019
OCT Outcomes									
Baseline (week 4)	179	195	No view	Lost to Follow-up	No view	No view due to worsening cataracts	261	299	302
Week 52	250	Lost to Follow-up	437	Lost to Follow-up	Lost to Follow-up	219- after cataract extraction	Lost to Follow-up	Expected in March 2019	Expected in May 2019

***AA: African American; IAI: Intravitreal Aflibercept Injection; PPV: Pars Plana Vitrectomy; TRD: Traction Retinal Detachment; PRP: Pan-retinal Photocoagulation**

Discussion

Our 1-year results indicate safety, moderate-term durability, and significant VA improvement after endolaserless vitrectomy with aflibercept for PDR-related VH. Through 52 weeks, endophthalmitis, progression of traction retinal detachment, iris/angle neovascularization, and neovascular glaucoma were not observed. Adverse events at any time through 52 weeks occurred infrequently and were more common in the q16week group. VA improved soon after surgery with a 52-week letter gain of 33 letters. VA loss at week 52 occurred in 5 eyes (3 from DME recurrence, 0 from proliferative consequences, and 2 of unclear etiology).

VA 52-week outcomes favored the q8week group with a 40 letter gain versus a 24 letter gain in the q16week group. While the safety and acuity outcomes tend to favor the q8week group, a larger cohort and longer follow-up is required to determine the optimal dosing regimen.

Our 1-year endolaserless PPV VA results are consistent with previous one year results from the DRIVE-UK study which retrospectively evaluated vitrectomy with endolaser for a non-clearing VH subgroup of 60 eyes (excluding traction retinal detachment) [14]. Other retrospective studies of vitrectomy with endolaser for PDR-related VH (without traction) yield no better visual outcomes than our results [14-17]. Aflibercept with endolaserless vitrectomy safety and efficacy results appear comparable to using endolaser while avoiding vitrectomy for the 3 q16week eyes and 1 q8week eye with recurrent vitreous hemorrhage by administering pro re nata (PRN) aflibercept and presumably reducing other endolaser PRP side-effects such as DME exacerbation or visual field compromise. Our visual field results are limited due to small numbers but indicate some overall visual field loss (statistically significant). Given the DRCR Protocol S finding of reduced visual field scores from years 2 to 5 in the ranibizumab group [8], planned longer-term evaluation is necessary in our cohort to document our long-term visual field outcomes. We also demonstrated macular thinning in both groups and a low incidence of OCT>300 um at 52 weeks. While much of our visual gain is likely due to clearance of vitreous hemorrhage by PPV alone, aflibercept-related macular thinning may result in greater acuity gains observed in the q8week group.

Post-operative wide-field fluorescein angiography, employed in our approach, is a key component for neovascularization monitoring. After endolaserless PPV, PDR progression at any time through 52 weeks, was observed in 21% and 29% of q8week and q16week eyes, respectively, despite mandatory aflibercept injections. Interestingly, absence of neovascularization at 52 weeks was found in 71% of q8week eyes but in only 35% of q16week eyes. These findings speak to the issue that while anti-VEGF therapy can cause regression of neovascularization, it is likely that neovascularization will recur without some form of maintenance anti-VEGF. While it has been proposed that PRP may be a more durable treatment for PDR and neovascularization than anti-VEGF therapy, results from our major PDR trials for eyes not requiring vitrectomy have not borne this out. Through 1 year, 65% and 6% of CLARITY study PRP eyes required additional PRP and vitrectomy, respectively [14]. Through 5 years, 54% and 22% of DRCR Protocol S PRP eyes developed vitreous hemorrhage and need for vitrectomy, respectively [8]. The above trials monitored neovascularization via clinical examination and did not monitor with wide-field or standard fluorescein angiography, which may account for potential under-treatment and relatively high rates of vitreous hemorrhage. The DRCR Protocol S required at least 1200 spots of laser in the PRP group which is significantly less than the 1600 spot requirement established by the DRS and ETDRS trials decades ago. Thus, under-treatment with PRP is another possible cause for relatively high rates of proliferative consequences in our more recent PDR trials. This may also limit the support for advocates of a "lighter endolaser PRP" during PPV. In the PROTEUS study, which evaluated PDR eyes with high-risk characteristics not requiring vitrectomy, complete neovascularization regression was observed in 44% in eyes receiving both PRP and ranibizumab versus only 25% in the PRP monotherapy group [9]. Thus far, evidence

does not support the notion that adding endolaser to aflibercept or endolaser alone would necessarily provide improved long-term durability or safety for PDR eyes requiring vitrectomy for vitreous hemorrhage. It is also possible that removal of the vitreous scaffold may be somewhat protective for proliferative consequences even without administering endolaser PRP.

Nevertheless, there understandably remains reticence for adopting endolaserless PPV especially for more advanced PDR. Aflibercept demonstrates superior outcomes to other anti-VEGF agents for DME eyes with worse VA and for regression of PDR [1,2,6]. In DRCR Protocol S, eyes with greater baseline severity of PDR demonstrated better visual outcomes with ranibizumab than PRP [18]. These data may reduce concerns for omitting endolaser for more severe PDR. Given the absence of any other anti-VEGF agent use for this endolaserless approach, it remains unclear whether aflibercept is the optimal agent. Concerns are escalated especially for patients at risk for non-compliance with follow-up visits [19] even within a structured clinical trial, such as DRCR Protocol S, only 66% of patients completed the 5-year visit [8]. Our 1-year noncompliance rates are equally concerning. One initially non-compliant patient returned later without visual compromise or complications. Longer-term follow-up of compliant and non-compliant endolaserless patients may help determine critical outcomes after poor adherence to visits. It is also concerning that half of our nonrandomized patients were noncompliant after undergoing PPV with endolaser. In addition to compliance concerns, cost, systemic health, and frequency of visits remain a consideration when choosing a treatment approach [8].

The strengths of our study include the prospective nature, use of ETDRS BCVA, modest but significant number randomized, two clinically relevant dosing regimens, visual field assessment, protocol specific PRN dosing criteria based on clinical, OCT, fundus photographic, and, importantly, wide-field fluorescein angiographic analyses. In addition, our inclusion criteria required that vitrectomy was indicated and planned prior to enrollment. Baseline acuities were wide ranged and our population is likely representative of real-world eyes.

The limitations of our study include a modest number and only 1-year data. Our study received approval to include 40 eyes with 3 years duration. This will address the ultimate safety of both dosing regimens and compliance rates. Other limitations include an absence of a control group such as standard or limited or "lighter" peripheral endolaser PRP, PRN dosing, or comparison to other anti-VEGF agents. Our randomized eyes with "simple" vitreous hemorrhage and exclusion of traction macular detachment may have a favorable prognosis with other therapies. Our study intends to evaluate safety and potential efficacy of this new surgical approach and is not intended in a smaller pilot study to make comparisons to vitrectomy with endolaser, observation, anti-VEGF injections without surgery etc.

Conclusion

Our favorable results do not necessarily support widespread adaptation of endolaserless vitrectomy. Additional study follow-up and widening experience will determine the continued balance and contemplation between anti-VEGF therapy and endolaser PRP [12].

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Siobhan Ortiz, Thomas Bailey, and Ken Ivey at Southeast Retina Center, provided technical and data support. Dr. Dennis Marcus has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Meeting Presentation

This work was presented at the American Society of Retina Specialists, Boston, MA-August 2017; Association for Research in Vision and Ophthalmology, Baltimore, MD-May 2017; American Academy of Ophthalmology, New Orleans, LA-November 2017 and American Society of Retina Specialists, Vancouver, BC-July 2018.

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Regeneron Pharmaceuticals Inc. was responsible for manufacturing and supplying the drug used in the study. The investigator-initiated study received clinical research grant support from Regeneron to conduct the trial. The sponsor was Southeast Retina Center and Dr. Marcus was responsible for the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, preparation, and approval of the manuscript. Regeneron, the funding organization, reviewed the manuscript prior to submission.

Conflict of Interest

Dr. Dennis M. Marcus has served as an advisor or consultant for Regeneron Pharmaceuticals, Genentech/Roche; as a speaker or member of the speakers bureau for Regeneron Pharmaceuticals; received grants for clinical research from Regeneron Pharmaceuticals; and reports pharmaceutical-sponsored clinical research from Allergan, Alcon, Aerpio, Kalvista, Ionis, Mylan, Samsung, Novartis, Opthea, Chenghdu, Clearside, Astellas, Allegro, Alimera, Ophthotech/Iveric, Outlook, Gemini, Genentech, ThromboGenics, Tyrogenex, Graybug, Topcon, Optos, Xplore, Gyroscope, Stealth Spiam, Aerie, Apellis, Roche, Novartis, OHR, Xplore, Regenxbio, Kodiak , Zeiss, and Regeneron Pharmaceuticals. Dr. Harinderjit Singh has received grants for clinical research from Regeneron Pharmaceuticals and reports pharmaceutical sponsored clinical research from Allergan, Alcon, Clearside, Astellas, Allegro, Alimera, Ophthotech Genentech, ThromboGenics, Tyrogenex, Apellis, Roche, Novartis, OHR, and Regeneron Pharmaceuticals. The remaining authors have no relevant financial disclosures. Dr. Lalane has received grants for clinical research and reports pharmaceutical-sponsored clinical research from Allergan, Alcon, Clearside, Astellas, Allegro, Alimera, Ophthotech, Genentech, ThromboGenics, Tyrogenex, Apellis, Roche, Novartis, OHR, Samsung, Ironside, Chengdhu, Mylan, and Regeneron Pharmaceuticals.

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