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COMPOUND NUMBER: PF-04523655

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00701181

PROTOCOL NO.: B0451004

PROTOCOL TITLE: A Phase II Prospective, Randomized, Multi-Center, Diabetic Macular Edema Dose Ranging, Comparator Study Evaluating the Efficacy and Safety of PF-04523655 versus Laser Therapy (DEGAS)

Study Centers: 43 centers in total: 1 in Denmark, 3 in Germany, 4 in India, 5 in Israel, 7 in Italy, 2 in Peru, 5 in United Kingdom, 16 in United States

Study Initiation Date and Primary Completion or Completion Dates:
23 June 2008 to 28 January 2011

The study was terminated prematurely.

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To evaluate the efficacy of 3 dose levels of PF-04523655 in improving visual acuity in subjects with diabetic macular edema (DME).

Secondary Objectives:

- To evaluate the safety and tolerability of PF-04523655 in subjects with DME.
- To evaluate the dosing schedule in maintaining the effect of PF-04523655 in subjects with DME.
- To evaluate changes in lesion morphology following administration of PF-04523655 by fundus photography (FP), fundus angiography (FA), and optical coherence tomography (OCT).

- To evaluate the efficacy of PF-04523655 on vision-related function and well being assessed using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25).

- To evaluate systemic exposure of PF-04523655 at 1 week following the first dose.

METHODS

Study Design: This was a Phase 2 prospective, randomized, multicenter, dose-ranging, laser photocoagulation comparator study evaluating the efficacy and safety of PF-04523655 in subjects with DME. Subjects with DME were stratified by screening visual acuity (<55 or ≥55 letters) and randomized to receive either PF-04523655 (0.4 mg, 1 mg, or 3 mg) or laser photocoagulation at a 1:1:1:1 ratio.

Subjects randomized to the PF-04523655 arms were to be treated with PF-04523655 every month via intravitreal (IVT) injection for a period of 6 months followed by treatment on an as needed (PRN) basis for additional 29 months. After the Month 6 visit, subjects were to be reviewed every month to assess the need for re-treatment with PF-04523655 until the Month 35 visit. Subjects were to be re-treated with PF-04523655 if they met the re-treatment criteria described in the protocol. Subjects randomized to the laser treatment were to be treated with laser photocoagulation at baseline and then assessed every 3 months for further laser treatment. Laser re-treatment was to be guided by the re-treatment criteria described in the protocol.

The Interim Analysis Review Committee (IARC) recommended that this trial be discontinued based upon internal pre-determined futility efficacy and subject discontinuation criteria. Since most subjects had not reached the Month 24 visit (original primary efficacy endpoint) at the time of study termination, study efficacy reporting was focused on Month 12 rather than Month 24.

Number of Subjects (Planned and Analyzed): A total of 160 subjects with DME were planned to be enrolled into the study, where the sample size for each of the PF-04523655 dose groups and the laser photocoagulation group was to be 40 subjects but could be adjusted to up to 70 subjects per group at the interim analyses. A total of 317 subjects were screened for participation in this study, and 46 subjects each were randomized to the PF-04523655 0.4 mg, 1 mg, and 3 mg groups and the laser photocoagulation group (a total of 184 subjects). All 184 subjects in the study were treated.

Diagnosis and Main Criteria for Inclusion: At the screening visit, subjects must have had a history of diabetes mellitus (Type 1 or Type 2), serum glycosylated hemoglobin (HbA1c) ≥5.5% and ≤12%, DME affecting the fovea consisting of an OCT central subfield retinal thickness ≥275 μm, reduced best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol of 20/40 (letter score of ≤73) or worse and up to 20/320 (letter score ≥24) or better in the study eye as a result of macular edema, and a BCVA in the fellow eye of 20/400. Subjects also must have had ocular media and adequate papillary dilation to allow good quality OCT and stereoscopic FP. Subjects were excluded if panretinal photocoagulation or macular photocoagulation was performed in

the study eye within 3 months of the screening visit, if they were at high risk of developing proliferative diabetic retinopathy, and if there was a history of DME for more than 2 years.

Study Treatment: In subjects randomized to PF-04523655, the study medication was to be administered once every month via IVT injection at doses ranging from 0.4, 1, and 3 mg for 6 months. After the Month 6 visit, subjects were to be administered PF-04523655 on a PRN basis according to re-treatment or rescue criteria with the final dose being administered at Month 35. Once randomized to a dose level, subjects remained at that same dose level for the duration of their participation in the study. For subjects randomized to laser photocoagulation, the treatment was to be administered according to a standardized photocoagulation technique.

PF-04523655 investigational drug product was formulated and supplied as a sterile solution for IVT injection. PF-04523655 drug product was formulated to deliver the specified dose levels when diluted as directed.

Efficacy Evaluations: The primary endpoint of this study was mean change from baseline (Day 0) at Month 24 in the BCVA score, as measured by ETDRS visual acuity protocol. Since most subjects did not reach the Month 24 visit at the time of study termination, evaluation of study efficacy was focused on Month 12 rather than Month 24.

The secondary efficacy endpoints of this study were as follows:

- Percent of subjects gaining ≥15 letters in BCVA score from baseline by scheduled study visit up to Month 36, as measured by the number of letters read correctly per ETDRS visual acuity protocol.
- Percent of subjects gaining ≥10 letters in BCVA score from baseline by scheduled study visit up to Month 36, as measured by the number of letters read correctly per ETDRS visual acuity protocol.
- Percent of subjects losing <15 letters in BCVA score from baseline by scheduled study visit up to Month 36, as measured by the number of letters read correctly per ETDRS visual acuity protocol.
- Mean changes in BCVA score from baseline by scheduled study visit up to Month 36, as measured by the number of letters read correctly per ETDRS visual acuity protocol.
- Mean changes in central subfield retinal thickness from baseline by scheduled study visit up to Month 36, as assessed by OCT and measured by a central reading center.
- Mean changes in macular volume from baseline by scheduled study visit up to Month 36, as assessed by OCT and measured by a central reading center.
- Mean changes in area of fluorescein leakage from baseline by scheduled study visit up to Month 36, as assessed by FA.

Pharmacokinetic and Patient-Reported Outcomes Evaluations:

Pharmacokinetic Evaluations: A secondary objective of this study was to evaluate the systemic exposure of PF-04523655 at 1 week following the first dose. Samples were taken for the determination of PF-04523655 plasma concentrations on Days 0 (pre-dose) and on Day 7 ± 2 days (post-dose). The samples were obtained only from subjects allocated to PF-04523655 arms. Plasma samples were analyzed for PF-04523655 concentrations using a validated analytical assay in compliance with Pfizer standard operating procedures.

Patient-Reported Outcomes Evaluations: The patient-reported outcome (PRO) endpoint for this study was the mean changes in NEI-VFQ-25 composite score and the 12 subscale scores from baseline to a scheduled study visit.

Safety Evaluations: Safety endpoints included the following:

- Incidence and severity of ocular adverse events (AEs), as identified by ophthalmic examination and/or spontaneously reported.

  Ocular AEs identified by ophthalmic examinations included:

  1. New or worsening findings of abnormalities from biomicroscopy of the anterior segment – lids, conjunctivae, cornea, anterior chamber, iris, and lens; presence/absence of anterior chamber inflammation; phakic status (ie, phakia, aphakia, or pseudophakia); posterior lens capsule status (ie, intact, open or absent);

  2. New or worsening findings of abnormalities from ophthalmoscopy of the posterior segment – vitreous body, optic nerve head, macular and peripheral retina; presence/absence of vitreous inflammation;

  3. An increase of intraocular pressure (IOP) at 60 minutes post-IVT injection that was 5 mm Hg greater than the pre-injection IOP was reported as an AE.

- Incidence and severity of systemic AEs, as identified by changes in vital signs, electrocardiogram (ECG), clinical laboratory abnormalities, and/or spontaneously reported.

Statistical Methods: The study planned to enroll 160 subjects. Forty subjects per group was to provide 78% power at a 1-sided 0.05 significance level to detect a 7-letter difference in mean changes of visual acuity between any of the PF-04523655 dose groups and the laser photocoagulation arm, assuming a standard deviation (SD) of 11.8 and a dropout rate of 15%. The sample size for the dose groups selected to be continued to study completion could be adjusted up to 70 subjects per group following any of the 3 interim analyses, which were planned to be performed when 120 subjects completed the Month 3, 6, and 12 visits. The objectives of sample size adjustment were to either increase the precision of the treatment-difference estimate or to detect a difference smaller than 7 letters. For example, an increase of sample size to 70 per group would have 74% power to detect a difference of 5 letters in mean changes of visual acuity between selected PF-04523655 dose groups and the

laser photocoagulation arm, assuming the same SD of 11.8 and same dropout rate of 15%. Such an upward sample size adjustment would increase the confidence of the data observed in this study, and reduce the risk of potential Phase 3 failure.

The intent-to-treat (ITT) population was used for all safety analyses and consisted of all enrolled subjects who received at least 1 study treatment.

Efficacy: The difference in mean BCVA change from baseline (Day 0) at Month 12 between any of the PF-04523655 dose groups and the laser photocoagulation arm was analyzed using an ANOVA model with treatment group and screening BCVA category as factors in the ITT population. Missing values were imputed using the last observation carried forward (LOCF) method. The null hypotheses of no difference between the groups were tested at a 1-sided 0.05 (2-sided 0.10) level of significance for non-confirmatory, internal decision-making purpose and therefore p-values were not adjusted for multiple comparisons.

For all other numeric secondary efficacy endpoints including mean changes from baseline in BCVA, central subfield retinal thickness, macular volume, and fluorescein leakage area by study visit, treatment-group comparisons between any of the PF-04523655 dose groups and the laser photocoagulation arm were also performed using the primary ANOVA model.

For percent of subjects gaining ≥15 BCVA letters, gaining ≥10 BCVA letters, and losing <15 BCVA letters, treatment-group comparisons between any of the PF-04523655 dose groups and the laser photocoagulation arm were performed using a Cochran-Mantel-Haenszel test stratified by screening BCVA category.

Pharmacokinetics: PF-04523655 plasma concentrations were listed for all subjects.

Safety: The treatment-emergent AE overall incidence rate and incidence rates by system organ class were tabulated by treatment group. The summary table for incidence by system organ class was further broken down by maximum severity and/or whether events were related to study treatment or injection procedure. Eye disorders were identified as disorders associated with either study eye, fellow eye, or both eyes.

Descriptive results were summarized for ocular safety measures (ie, refractive error, IOP, intraocular inflammation, posterior lens status, biomicroscopy [anterior segment], ophthalmoscopy [posterior segment]) and other safety measures (ie, vital signs, ECG, and laboratory test results).

Patient-Reported Outcomes: The difference in mean NEI-VFQ-25 composite score and subscale scores change from baseline between any of the PF-04523655 dose groups and the laser photocoagulation arm at each visit were analyzed using the primary ANOVA model.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is provided in Table 1. No subjects completed the 36-month study period since the study was terminated early by the sponsor. The most common reasons for discontinuation were that the study was terminated by the sponsor (95 subjects), insufficient clinical response (42 subjects), and an

AE (19 subjects; 3 additional subjects discontinued due to AEs related to insufficient clinical response, 1 of which was considered to be related to study treatment; 1 additional subject died and is listed in the AE section as having discontinued due to an AE) (Table 1). At Month 6 and Month 12, all of the PF-04523655 treatment groups had higher discontinuation rates than the laser photocoagulation group. Among the PF-04523655 groups, the 0.4 mg group had the highest discontinuation rate, and the 3 mg group had the lowest discontinuation rate up to Month 12.

Table 1. Subject Disposition

	----------PF-04523655----------			Laser	Total
Number (%) of Subjects	**0.4 mg**	**1 mg**	**3 mg**	**Photocoagulation**	
Screened N = 317					
Assigned to study treatment	46	46	46	46	184
Treated	46	46	46	46	184
Completed	0	0	0	0	0
Discontinued	46 (100)	46 (100)	46 (100)	46 (100)	184 (100)
Subject died	0	0	1	1	2
Related to study drug	33	34	36	34	137
Insufficient clinical response	14	14	10	4	42
Study terminated by sponsor	19	20	26	30	95
Not related to study drug	13	12	9	11	45
AE	5	5[a]	6[b]	3[c]	19
Lost to follow-up	0	2	0	1	3
Other	2	3	0	5	10
Protocol violation	2	0	0	0	2
No longer willing to participate	4	2	3	2	11

AE = adverse event
[a] Two additional subjects discontinued due to AEs related to insufficient clinical response.
[b] One additional subject died due to an AE.
[c] One additional subject discontinued due to a treatment-related AE related to insufficient clinical response.

The majority of subjects in each treatment group were male. The mean age was similar between treatment groups (61.8 years overall). The majority of subjects were white (78.3%). All subjects had been diagnosed with diabetic retinal edema (DME), with a mean duration of 32.8 months in the PF-04523655 0.4 mg group, 30.0 months in the PF-04523655 1 mg group, 35.2 months in the PF-04523655 3 mg group, and 29.6 months in the laser photocoagulation group. Except for the PF-04523655 0.4 mg group, more subjects in each group had the right eye as the study eye. The BCVA of the study eye was similar between treatment groups and was ≥55 letters in a majority of subjects in each treatment group.

Efficacy Results:

Primary: The primary endpoint evaluated in this study was mean change from baseline at Month 12 in the BCVA score. A summary of the change in BCVA score from baseline at Month 12 (LOCF) for the study eye is provided in Table 2. The least square (LS) mean BCVA change from baseline at Month 12 in the PF-04523655 3 mg group (5.77 letters) showed a statistically significant difference from the laser photocoagulation group (2.39 letters) at a 2-sided significance level of 0.1 (p = 0.0779). The differences between the PF-04523655 0.4 mg (2.21 letters) and laser photocoagulation groups and between the

PF-04523655 1 mg (4.19 letters) and laser photocoagulation groups were not statistically significant (p = 0.9269 and p = 0.3452, respectively).

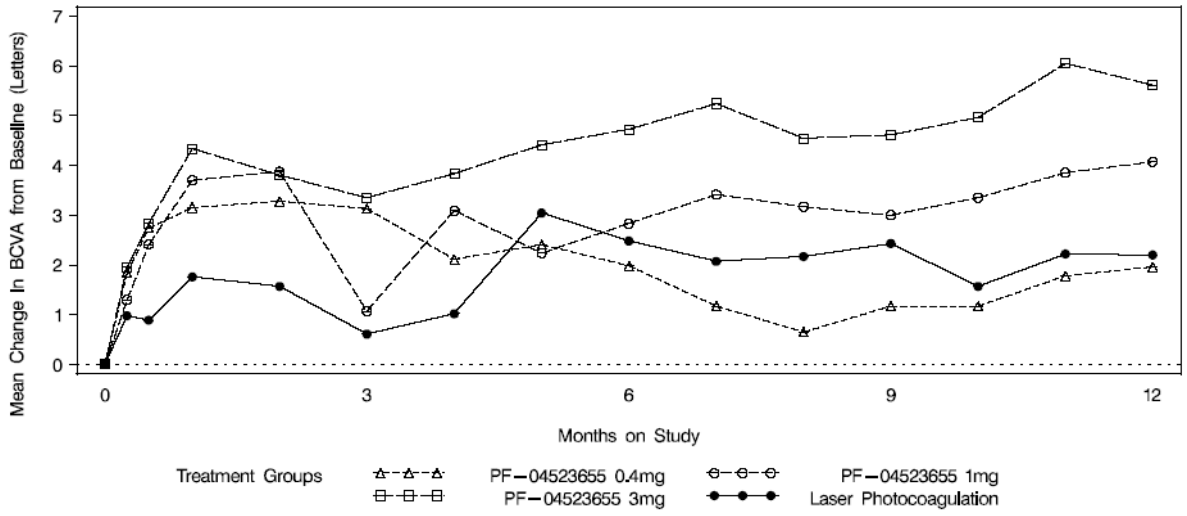
Table 2. Change in BCVA (letters) from Baseline at Month 12 (LOCF), Study Eye, ITT Population

	----------PF-04523655----------			Laser
	0.4 mg N = 46	**1 mg** N = 46	**3 mg** N = 46	**Photocoagulation** N = 46
Raw values				
Mean (SD)	59.39 (13.73)	60.85 (14.54)	62.17 (13.40)	59.93 (15.84)
Median (range)	60.50 (30 to 85)	61.50 (19 to 83)	62.00 (19 to 85)	64.00 (0 to 82)
Change from baseline				
Mean (SD)	1.96 (9.45)	4.07 (10.23)	5.61 (9.86)	2.20 (6.60)
Median (range)	1.00 (-25 to 23)	4.50 (-36 to 24)	6.00 (-23 to 30)	1.50 (-18 to 15)
LS mean (SE)	2.21 (1.37)	4.19 (1.35)	5.77 (1.36)	2.39 (1.36)
Treatment comparison to laser				
LS mean difference	-0.18	1.81	3.38	
90% CI	-3.33, 2.98	-1.35, 4.96	0.23, 6.53	
p-value[a]	0.9269	0.3452	0.0779	

BCVA = best corrected visual acuity; LOCF = last observation carried forward; ITT = intent-to-treat; SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval
[a] P-value was based on ANOVA model with treatment group and screening BCVA category as factors.

Secondary: In all treatment groups, within the first month there was a rapid increase in BCVA scores from baseline. The scores continued to slowly increase in PF-04523655 1 mg and 3 mg dose groups through Month 12. The positive correlation between PF-04523655 dose levels and the improvement in BCVA from baseline was maintained from Month 6 through Month 12 (Figure 1).

Figure 1. Mean Change in Visual Acuity from Baseline (LOCF) by Study Visit, Study Eye, ITT Population



LOCF = last observation carried forward; ITT = intent-to-treat; BCVA = best corrected visual acuity

A summary of the percentages of subjects with improvements or deteriorations in BCVA letters using the LOCF method at Month 12 in the ITT population is provided in Table 3. The total number of subjects who gained ≥15 letters at Month 12 was 4 (8.7%) subjects in the PF-04523655 0.4 mg group, 5 (10.9%) subjects in the PF-04523655 1 mg group, 8 (17.4%) subjects in the PF-04523655 3 mg group, and 1 (2.2%) subject in the laser photocoagulation group.

The total number of subjects who gained ≥10 letters at Month 12 was 10 (21.7%) in the PF-04523655 0.4 mg group, 14 (30.4%) in the PF-04523655 1 mg group, 13 (28.3%) in the PF-04523655 3 mg group, and 8 (17.4%) in the laser photocoagulation group.

The total number of subjects that lost ≥15 letters at Month 12 was 3 (6.5%) in the PF-04523655 0.4 mg group, 1 (2.2%) in the PF-04523655 1 mg group, 2 (4.3%) in the PF-04523655 3 mg group, and 1 (2.2%) in the laser photocoagulation group.

Table 3. Percentages of Subjects with Improvement or Deterioration in BCVA Letters at Month 12 (LOCF), Study Eye, ITT Population

	----------PF-04523655----------			
	0.4 mg N = 46	**1 mg** N = 46	**3 mg** N = 46	**Laser Photocoagulation** N = 46
Loss ≥15 letters, n (%)	3 (6.5)	1 (2.2)	2 (4.3)	1 (2.2)
Loss ≥10 to <15 letters, n (%)	1 (2.2)	0	0	1 (2.2)
Loss ≥5 to <10 letters, n (%)	5 (10.9)	8 (17.4)	3 (6.5)	3 (6.5)
Change with +/- 4 letters, n (%)	22 (47.8)	14 (30.4)	14 (30.4)	26 (56.5)
Gain ≥5 to <10 letters, n (%)	5 (10.9)	9 (19.6)	14 (30.4)	7 (15.2)
Gain ≥10 to <15 letters, n (%)	6 (13.0)	9 (19.6)	5 (10.9)	7 (15.2)
Gain ≥15 letters, n (%)	4 (8.7)	5 (10.9)	8 (17.4)	1 (2.2)
15-letter gainer[a] proportion difference from laser, %	6.5	8.7	15.2	
90% CI, %	-1.2, 14.2	0.4, 17.0	5.4, 25.1	
p-value[b]	0.189	0.099	0.016	
10-letter gainer[c] proportion difference from laser, %	4.3	13.0	10.9	
90% CI, %	-9.2, 17.9	-1.4, 27.5	-3.4, 25.1	
p-value[b]	0.607	0.154	0.219	
15-letter loser[d] proportion difference from laser, %	4.3	0.0	2.2	
90% CI, %	-2.6, 11.3	-5.0, 5.0	-3.9, 8.3	
p-value[b]	0.320	0.989	0.575	

BCVA = best corrected visual acuity; LOCF = last observation carried forward; ITT = intent-to-treat; CI = confidence interval

[a] 15-letter gainer: subjects who gained ≥15 letters in BCVA compared to baseline.

[b] P-value based on a Cochran-Mantel-Haenszel chi-square test stratified by screening BCVA category (<55 and ≥55).

[c] 10-letter gainer: subjects who gained ≥10 letters in BCVA compared to baseline.

[d] 15-letter loser: subjects who lost ≥15 letters in BCVA compared to baseline.

A summary of retinal central subfield thickness and its change from baseline (LOCF and observed) at Month 12 is provided in Table 4. The LS mean retinal central subfield thickness change from baseline at Month 12 (LOCF) in the laser photocoagulation group was -104 μm and the differences for the PF-04523655 0.4, 1, and 3 mg groups compared to the laser photocoagulation group were 57 (90% CI: 2 to 112), 84 (90% CI: 29 to 139), and 41 (90% CI: -14 to 96) μm, respectively. The mean change in retinal central subfield thickness profile from baseline through Month 12 (LOCF) showed that the laser photocoagulation group had a greater reduction in retinal central subfield thickness than all PF-04523655 dose groups between Months 4 and 12.

Table 4. Summary of Retinal Central Subfield Thickness (μm) and its Change from Baseline at Month 12, Study Eye, ITT Population

	PF-04523655			Laser Photocoagulation
	0.4 mg	1 mg	3 mg	
LOCF				
Number of subjects	46	46	46	46
Raw values				
Mean (SD)	435.1 (173.7)	437.3 (212.4)	392.9 (177.5)	361.0 (146.5)
Median (range)	417.0 (167.0 to 1012)	403.0 (151.0 to 1175)	350.5 (149.0 to 923.0)	369.5 (91.0 to 674.0)
Change from baseline				
Mean (SD)	-38.8 (155.6)	-16.2 (171.2)	-58.0 (170.8)	-98.0 (144.4)
Median (range)	-11.5 (-614 to 193.0)	-3.0 (-433 to 360.0)	-71.5 (-428 to 322.0)	-79.5 (-750 to 127.0)
LS mean (SE)	-46.65 (23.94)	-20.12 (23.66)	-62.90 (23.71)	-103.9 (23.78)
Treatment difference from laser				
LS mean difference	57.22	83.75	40.97	
90% CI	2.10, 112.35	28.63, 138.88	-14.13, 96.08	
p-value[a]	0.0878	0.0129	0.2205	
Observed				
Number of subjects	19	26	30	35
Raw values				
Mean (SD)	357.0 (120.9)	383.1 (181.3)	328.8 (122.7)	349.1 (154.5)
Median (range)	356.0 (167.0 to 609.0)	352.5 (151.0 to 780.0)	292.0 (149.0 to 589.0)	341.0 (91.0 to 674.0)
Change from baseline				
Mean (SD)	-70.4 (141.3)	-49.8 (175.6)	-107 (153.1)	-115 (156.1)
Median (range)	-55.0 (-444 to 163.0)	-42.0 (-433 to 330.0)	-101 (-428 to 263.0)	-86.0 (-750 to 127.0)
LS mean (SE)	-90.46 (35.81)	-62.86 (30.35)	-110.0 (27.94)	-123.7 (26.03)
Treatment difference from laser				
LS mean difference	33.25	60.85	13.68	
90% CI	-39.40, 105.90	-4.91, 126.62	-49.55, 76.92	
p-value[a]	0.4492	0.1277	0.7202	

ITT = intent-to-treat; SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval; LOCF = last observation carried forward; ANOVA = analysis of variance; BCVA = best corrected visual acuity
[a] P-value is based on an ANOVA model with treatment group and screening BCVA category as factors.

The LS mean total retinal volume change from baseline at Month 12 in the laser photocoagulation group was -0.8 mm^3 and the differences for the PF-04523655 0.4, 1, and 3 mg groups compared to the laser photocoagulation group were -0.28, 0.38, and 0.22 mm^3, respectively.

A summary of the area of fluorescein leakage within the grid and within the center subfield and their change from baseline at Month 12 is provided in Table 5. The LS mean change from baseline in area of fluorescein leakage within the grid at Month 12 in the laser photocoagulation group was -1.65 disc area (DA) and the differences for the PF-04523655 0.4, 1, and 3 mg groups compared to the laser photocoagulation group were 1.20, 1.26, and 0.61 DA, respectively. The LS mean change from baseline in area of fluorescein leakage within the center subfield at Month 12 in the laser photocoagulation group was -0.05 DA and

the differences for the PF-04523655 0.4, 1, and 3 mg groups compared to the laser photocoagulation group were -0.01, 0.06, and 0.02 DA, respectively.

The distribution of change in fluorescein leakage severity at Month 12 showed that a majority of subjects had less or stable leakage in all treatment groups. The LS mean area of retinal thickening within the grid change from baseline at Month 12 in the laser photocoagulation group was -1.06 DA and the differences for the PF-04523655 0.4, 1, and 3 mg groups compared to the laser photocoagulation group were 1.68, 1.56, and -0.05 DA, respectively.

Table 5. Summary of Area of Fluorescein Leakage within Grid (DA) and within Center Subfield (DA) and its Change from Baseline (Observed) at Month 12, Study Eye, ITT Population

	----------PF-04523655----------			Laser
	0.4 mg	**1 mg**	**3 mg**	**Photocoagulation**
Within Grid				
Raw values				
Number of subjects	16	23	27	32
Mean (SD)	6.68 (4.80)	7.96 (4.05)	5.91 (3.89)	6.68 (4.48)
Median (range)	5.54 (0.29 to 15.28)	8.60 (1.82 to 14.35)	5.16 (0.35 to 14.00)	6.26 (0.04 to 15.28)
Change from baseline				
Number of subjects	16	22	27	32
Mean (SD)	-0.31 (1.64)	-0.28 (2.14)	-1.02 (2.93)	-1.53 (2.67)
Median (range)	-0.17 (-4.97 to 2.04)	0.15 (-5.54 to 4.88)	-0.57 (-10.8 to 2.44)	-0.68 (-8.68 to 3.71)
LS mean (SE)	-0.45 (0.63)	-0.39 (0.53)	-1.04 (0.48)	-1.65 (0.45)
Treatment difference from laser				
LS mean difference	1.20	1.26	0.61	
90% CI	-0.06, 2.46	0.12, 2.40	-0.47, 1.69	
p-value[a]	0.1184	0.0694	0.3522	
Within Center Subfield				
Raw values				
Number of subjects	16	23	27	32
Mean (SD)	0.38 (0.13)	0.40 (0.10)	0.37 (0.15)	0.35 (0.15)
Median (range)	0.44 (0.00 to 0.44)	0.44 (0.00 to 0.44)	0.44 (0.00 to 0.44)	0.44 (0.00 to 0.44)
Change from baseline				
Number of subjects	16	22	27	32
Mean (SD)	-0.06 (0.13)	0.01 (0.09)	-0.03 (0.14)	-0.05 (0.14)
Median (range)	0.00 (-0.44 to 0.00)	0.00 (-0.10 to 0.38)	0.00 (-0.44 to 0.34)	0.00 (-0.39 to 0.26)
LS mean (SE)	-0.06 (0.03)	0.01 (0.03)	-0.02 (0.02)	-0.05 (0.02)
Treatment difference from laser				
LS mean difference	-0.01	0.06	0.02	
90% CI	-0.07, 0.06	0.00, 0.12	-0.03, 0.08	
p-value[a]	0.8472	0.1057	0.4940	

DA = disc area; ITT = intent-to-treat; SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval; ANOVA = analysis of variance; BCVA = best corrected visual acuity
[a] P-value is based on an ANOVA model with treatment group and screening BCVA category as factors.

Pharmacokinetic and Patient-Reported Outcomes Results:

Pharmacokinetic Results: There were 255 plasma samples (128 Day 0 and 127 Week 1 samples) obtained from 131 subjects. PF-04523655 plasma concentrations were uniformly below the lower limit of quantitation (LLOQ), with 5 exceptions. The highest plasma concentration observed was 1.08 ng/mL in a sample taken prior to administration of PF-04523655. All other Day 0 samples had assayed concentrations below the LLOQ. The other 4 samples had concentrations of PF-04523655 at or near the LLOQ (0.1 ng/mL) at 1 week after administration of study drug. Four of the 5 samples with measurable PF-04523655 concentrations were from samples that were evaluated after the documented time for stability.

Patient-Reported Outcomes Results: The mean NEI-VFQ-25 Composite Scores at baseline were similar across the 4 groups: 75.2, 69.9, 70.6, and 75.2 for the PF-04523655 0.4 mg, 1 mg, 3 mg, and the laser photocoagulation groups, respectively.

Table 6 summarizes the adjusted mean changes of the NEI-VFQ-25 Composite Scores over time for the 4 treatment groups. The data showed the following:

- For the subjects in the PF-04523655 0.4 mg and 3 mg groups who remained in the study, their NEI-VFQ-25 scores tended to improve over time, while little changes were seen in the subjects who remained in the PF-04523655 1 mg and laser photocoagulation groups;

- The improvements for the PF-04523655 0.4 mg and 3 mg groups were relatively small at first; however, by Months 12 to 18, their improvements reached the minimum clinical meaningful threshold of 4 to 6 point for neovascular AMD.

Table 6. Least Square Mean Changes of NEI-VFQ-25 Composite Scores

	----------PF-04523655----------			Laser
LS Mean Changes (standard error)	**0.4 mg**	**1 mg**	**3 mg**	**Photocoagulation**
Month 3	3.3 (1.9)	1.7 (2.0)	3.6 (1.9)	1.7 (1.8)
Month 6	6.9 (2.5)	1.8 (2.6)	5.2 (2.5)	-0.2 (2.2)
Month 12	7.4 (2.9)	0.4 (2.8)	4.1 (2.5)	1.2 (2.1)
Month 18	12.2 (3.9)	2.5 (3.9)	7.8 (3.1)	-1.0 (2.8)

NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire-25; LS = least square

For the NEI-VFQ-25 Composite Score, the LS mean changes from baseline showed that the PF-04523655 0.4 mg and 3 mg groups had better numerical results than the laser photocoagulation group; the differences were statistically significant for the 0.4 mg group at Months 6, 12, and 18, and for 3 mg group at Month 18.

Safety Results: Most subjects in the study reported a treatment-emergent AE, with a slightly lower percentage in the laser photocoagulation group compared to the PF-04523655 groups (91.3%, 93.5%, and 95.7% in the 0.4 mg, 1 mg, and 3 mg PF-04523655 groups, respectively, and 84.8% in the laser photocoagulation group). The majority of these AEs were considered to be unrelated to study treatment.

The majority of AEs in the laser photocoagulation group were considered to be unrelated to the procedure (2/237 AEs were related to the procedure in 2 [4.3%] subjects).

A total of 28 (60.9%), 22 (47.8%), and 25 (54.3%) subjects in the PF-04523655 0.4 mg, 1 mg, and 3 mg groups, respectively, reported AEs related to the injection procedure (38/178, 29/279, and 41/252 events in the PF-04523655 0.4 mg, 1 mg, and 3 mg groups, respectively).

The majority of AEs reported in this study were mild or moderate in severity. Treatment-emergent AEs that occurred in ≥5% of subjects in either treatment group are presented in Table 7. The most common events reported included post-injection IOP increased in the study eye, hypertension, conjunctival hemorrhage of the study eye, retinal hemorrhage of the study eye, and nasopharyngitis.

The incidence rate of endophthalmitis in the PF-04523655 0.4 mg and 3 mg groups was 0.2% (1 subject in each group). In 1 of the subjects, the affected eye was eviscerated. There were no cases of endophthalmitis in the PF-04523655 1 mg group.

The event of IOP increased in the study eye was more common in the PF-04523655 groups. All of the events in the PF-04523655 groups were considered to be related to the injection procedure. The high rates of increased IOP in the PF-04523655 groups were likely due to the criterion in the study protocol, which required investigators to report any observations of post injection IOP increase >5 mm Hg around 1 hour post-injection as AEs.

Table 7. Summary of Treatment-Emergent Adverse Events (All Causalities) in ≥5% of Subjects in Any Treatment Group

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System Organ Class Preferred Term	PF-04523655 0.4 mg n (%)	PF-04523655 1 mg n (%)	PF-04523655 3 mg n (%)	Laser Photocoagulation n (%)
Blood and lymphatic system disorders	1 (2.2)	4 (8.7)	2 (4.3)	2 (4.3)
Anemia	1 (2.2)	4 (8.7)	2 (4.3)	0
Cardiac disorders	4 (8.7)	4 (8.7)	7 (15.2)	6 (13.0)
Cardiac failure congestive	0	1 (2.2)	3 (6.5)	3 (6.5)
Eye disorders	28 (60.9)	34 (73.9)	30 (65.2)	30 (65.2)
Cataract cortical, both eyes	0	0	3 (6.5)	0
Cataract nuclear, fellow eye	1 (2.2)	3 (6.5)	2 (4.3)	1 (2.2)
Cataract nuclear, study eye	1 (2.2)	3 (6.5)	2 (4.3)	1 (2.2)
Cataract subcapsular, study eye	2 (4.3)	3 (6.5)	1 (2.2)	1 (2.2)
Conjunctival hemorrhage, study eye	8 (17.4)	6 (13.0)	5 (10.9)	2 (4.3)
Corneal erosion, both eyes	0	0	3 (6.5)	0
Diabetic retinopathy, study eye	1 (2.2)	1 (2.2)	2 (4.3)	3 (6.5)
Macular edema, fellow eye	4 (8.7)	4 (8.7)	1 (2.2)	1 (2.2)
Maculopathy, study eye	1 (2.2)	3 (6.5)	0	4 (8.7)
Ocular vascular disorder, study eye	1 (2.2)	3 (6.5)	2 (4.3)	4 (8.7)
Punctate keratitis, study eye	1 (2.2)	0	0	3 (6.5)
Retinal exudates, fellow eye	1 (2.2)	2 (4.3)	1 (2.2)	3 (6.5)
Retinal exudates, study eye	0	3 (6.5)	1 (2.2)	1 (2.2)
Retinal hemorrhage, fellow eye	0	1 (2.2)	4 (8.7)	2 (4.3)
Retinal hemorrhage, study eye	4 (8.7)	2 (4.3)	4 (8.7)	3 (6.5)
Vision blurred, both eyes	0	3 (6.5)	0	0
Vitreous disorder, study eye	2 (4.3)	3 (6.5)	0	0
Vitreous hemorrhage, fellow eye	1 (2.2)	1 (2.2)	2 (4.3)	4 (8.7)
Vitreous hemorrhage, study eye	2 (4.3)	4 (8.7)	0	3 (6.5)
Gastrointestinal disorders	5 (10.9)	10 (21.7)	5 (10.9)	6 (13.0)
Vomiting	3 (6.5)	1 (2.2)	1 (2.2)	1 (2.2)
Infections and infestations	14 (30.4)	15 (32.6)	17 (37.0)	16 (34.8)
Cellulitis	2 (4.3)	1 (2.2)	1 (2.2)	3 (6.5)
Nasopharyngitis	4 (8.7)	3 (6.5)	2 (4.3)	3 (6.5)
Pneumonia	0	0	3 (6.5)	0
Sinusitis	0	3 (6.5)	0	2 (4.3)
Upper respiratory tract infection	2 (4.3)	3 (6.5)	4 (8.7)	2 (4.3)
Urinary tract infection	1 (2.2)	2 (4.3)	0	4 (8.7)
Injury, poisoning and procedural complications	6 (13.0)	5 (10.9)	7 (15.2)	11 (23.9)
Fall	1 (2.2)	1 (2.2)	1 (2.2)	5 (10.9)

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row.
Medical Dictionary for Regulatory Activities (MedDRA) (v13.1) coding dictionary applied.

Table 7. Summary of Treatment-Emergent Adverse Events (All Causalities) in ≥5% of Subjects in Any Treatment Group

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System Organ Class Preferred Term	PF-04523655 0.4 mg n (%)	PF-04523655 1 mg n (%)	PF-04523655 3 mg n (%)	Laser Photocoagulation n (%)
Investigations	25 (54.3)	28 (60.9)	29 (63.0)	15 (32.6)
Blood creatinine increased	0	6 (13.0)	3 (6.5)	2 (4.3)
Blood glucose increased	1 (2.2)	4 (8.7)	2 (4.3)	3 (6.5)
Blood pressure increased	3 (6.5)	0	0	1 (2.2)
Blood urea increased	0	4 (8.7)	2 (4.3)	1 (2.2)
Glycosylated hemoglobin increased	1 (2.2)	5 (10.9)	2 (4.3)	3 (6.5)
Intraocular pressure increased, both eyes	0	0	3 (6.5)	0
Intraocular pressure increased, fellow eye	2 (4.3)	1 (2.2)	3 (6.5)	3 (6.5)
Intraocular pressure increased, study eye	18 (39.1)	20 (43.5)	22 (47.8)	1 (2.2)
Metabolism and nutrition disorders	4 (8.7)	10 (21.7)	9 (19.6)	7 (15.2)
Hypercholesterolemia	1 (2.2)	4 (8.7)	2 (4.3)	1 (2.2)
Hypoglycemia	1 (2.2)	2 (4.3)	0	3 (6.5)
Nervous system disorders	3 (6.5)	5 (10.9)	10 (21.7)	6 (13.0)
Headache	0	1 (2.2)	4 (8.7)	2 (4.3)
Vascular disorders	4 (8.7)	7 (15.2)	10 (21.7)	5 (10.9)
Hypertension	4 (8.7)	7 (15.2)	9 (19.6)	4 (8.7)

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row.
Medical Dictionary for Regulatory Activities (MedDRA) (v13.1) coding dictionary applied.

Worsening of existing cataracts or newly diagnosed cataracts were reported in all treatment groups. The number of cataracts (including cortical, nuclear, and posterior subcapsular types) in the study eye reported as AEs in the PF-04523655 0.4 mg, 1 mg, 3 mg and laser photocoagulation groups was 5, 9, 10, and 3, respectively. Of these, there were 2 mild posterior subcapsular cataracts that were considered as treatment-related and were attributed to PF-04523655. Both subjects continued to receive PF-04523655 without progression of the posterior subcapsular cataracts, and both subjects stayed in the study until it was terminated by the sponsor.

A total of 5 (10.9%), 7 (15.2%), 7 (15.2%), and 4 (8.7%) subjects in the PF-04523655 0.4 mg, 1 mg, and 3 mg groups and the laser photocoagulation group, respectively, were discontinued due to AEs. One discontinuation in the laser photocoagulation group with an event of visual acuity reduced in the study eye was considered to be related to study treatment. Two discontinuations in the PF-04523655 0.4 mg group (endophthalmitis and transient blindness in the study eye) and 1 discontinuation in the PF-04523655 3 mg group (endophthalmitis) were considered to be related to the injection procedure. The rest of the AEs were considered unrelated to either study treatment or injection procedure and include: ocular vascular disorder in the study eye, retinal neovascularization in the study eye, drug effect decreased in the study eye, vitreous hemorrhage in the study eye, retinal detachment in the study eye, diabetic retinopathy in the study eye, diabetic retinal edema in the study eye, cystoid macular edema in the study eye, macular edema in the study eye, hypertension, cardiac arrest, ischemic cardiomyopathy, pulmonary congestion, dyspnea and fall. Permanent discontinuations due to AEs are summarized in Table 8.

Table 8. Permanent Discontinuations Due to Adverse Events

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Sex/age (years)	Preferred Term	Severity	Outcome	Causality
PF-04523655 0.4 mg Group				
F/70	Endophthalmitis, study eye	Severe	Resolved	Injection/procedure related
M/59	Blindness transient, study eye	Severe	Resolved	Injection/procedure related
M/47	Ocular vascular disorder, study eye	Moderate	Still present	Disease under study
F/68	Pulmonary congestion	Moderate	Resolved	Other illness – hypertension
	Hypertension	Moderate	Resolved	Other illness – patient suffers from basic hypertension that went out of control
M/66	Drug effect decreased, study eye	Moderate	Still present	Disease under study
PF-04523655 1 mg Group				
M/61	Vitreous hemorrhage, study eye	Moderate	Still present	Other illness – diabetic retinopathy
M/51	Retinal detachment, study eye	Severe	Still present	Other – unknown
M/68	Retinal neovascularization, study eye	Moderate	Still present	Disease under study
F/63	Retinal neovascularization, study eye	Moderate	Still present	Other illness – diabetes
M/60	Diabetic retinopathy, study eye	Severe	Still present	Disease under study
M/57[a]	Macular edema, study eye	Moderate	Still present	Disease under study
M/57[a]	Diabetic retinal edema, study eye	Severe	Still present	Disease under study
PF-04523655 3 mg Group				
F/72	Endophthalmitis, study eye	Moderate	Resolved	Injection/procedure related
F/49	Diabetic retinopathy, study eye	Moderate	Still present	Other – progression of diabetic retinopathy
M/64	Ischemic cardiomyopathy	Moderate	Still present	Other – hypertension, diabetes, dyslipidemia
M/67	Dyspnea	Moderate	Resolved	Other – shortness of breath
M/45	Diabetic retinopathy, study eye	Severe	Still present	Disease under study
M/58[b]	Cardiac arrest	Severe	Resolved	Other – cardiac arrest resulting in death
M/60	Cystoid macular edema, study eye	Moderate	Still present	Disease under study
Laser Photocoagulation Group				
M/77	Fall	Severe	Unknown	Other illness – subject has history of arthritis
M/53	Diabetic retinopathy, study eye	Moderate	Resolved	Disease under study
M/61	Ocular vascular disorder, study eye	Severe	Still present	Disease under study
M/68[a]	Visual acuity reduced, study eye	Severe	Still present	Study drug

Age was at screening. Medical Dictionary for Regulatory Activities (v13.1) coding dictionary was applied.
F = female; M = male.
[a] Subject was listed in the discontinuation listing as having discontinued due to insufficient clinical response.
[b] Subject was listed in the discontinuation listing as having discontinued due to death.

A total of 3 (6.5%), 2 (4.3%), 5 (10.9%), and 1 (2.2%) subjects in the PF-04523655 0.4 mg, 1 mg, and 3 mg groups and the laser photocoagulation group, respectively, had a dose reduction or temporary discontinuation due to AEs.

There were 2 deaths reported during the study. A 58-year-old male in the PF-04523655 3 mg group died on Study Day 439 (post-therapy) due to cardiac arrest. This event was not related to study treatment or the injection procedure. A 93-year-old female in the laser photocoagulation group died on Study Day 892 (post-therapy) due to recurrent aspiration pneumonia. This event was considered to be caused by maturity and a history of chronic obstructive pulmonary disorder and was listed as an AE leading to discontinuation.

A total of 8 (17.4%) subjects in the PF-04523655 0.4 mg group, 12 (26.1%) subjects in the PF-04523655 1 mg group, 17 (37.0%) subjects in the PF-04523655 3 mg group, and 10 (21.7%) subjects in the laser photocoagulation group reported serious adverse events (SAEs). An additional subject in the laser photocoagulation group reported an SAE that was not included in the clinical database, but was included in the safety database. An additional 4 subjects reported SAEs prior to randomization (pancreatic tumor, hypertensive crisis and apoplexy, flu, and hypertension). None of the SAEs were considered related to study treatment. Two subjects in the PF-04523655 0.4 mg group (1 subject with an event of endophthalmitis and another subject with events of visual impairment and transient blindness), 1 subject in the PF-04523655 1 mg group (with an event of blindness), and 1 subject in the PF-04523655 3 mg group (with an event of endophthalmitis) reported SAEs considered to be related to the injection procedure. A summary of SAEs is provided in Table 9. The rest of the SAEs were considered unrelated to either study treatment or injection procedure and include: retinal detachment, cataract subcapsular, cataract, coronary artery disease, coronary artery occlusion, cardiac arrest, cardiac failure congestive, cerebrovascular accident, atrial fibrillation, myocardial infarction, acute myocardial infarction, myocardial ischemia, ischemic cardiomyopathy, ischemic stroke, pulmonary congestion, pneumonia, pneumonia aspiration, chronic obstructive pulmonary disease, hypertension, hyperkalemia, hyperglycemia, hypoglycemia, blood creatinine increased, blood creatine phosphokinase increased, blood osmolarity decreased, anemia, renal failure, renal failure acute, renal failure chronic, renal cancer, liver disorder, hepatic encephalopathy, prostate cancer, subdural hematoma, diabetes mellitus, diabetic foot, myalgia, vertigo, sepsis, staphylococcal infection, streptococcal bacteremia, localized infection, post procedural infection, rhabdomyolysis, cellulitis, osteomyelitis, gastroenteritis, colitis ulcerative, neuropathic ulcer, skin ulcer, fall, lower limb fracture, femur fracture, rib fracture, road traffic accident, joint dislocation, impaired healing, gangrene, abscess limb, laryngeal cyst, mania, dyspnea, deafness neurosensory, and syncope.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
PF-04523655 0.4 mg Group					
M/51	34	Coronary artery disease	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
F/70	1	Endophthalmitis	Unrelated/ Unrelated[a]	Recovered/ Resolved with sequelae	Disability; important medical event
M/60	148	Visual impairment	Unrelated/ Unrelated[a]	Recovered/ Resolved	Important medical event
	204	Blindness transient	Unrelated/ Unrelated[a]	Recovered/ Resolved	Important medical event
	253	Blindness transient	Unrelated/ Unrelated[a]	Recovered/ Resolved	Important medical event
F/59	197	Renal failure	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/44	245	Rhabdomyolysis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Renal failure acute	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Hyperkalemia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Hypertension	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	365	Myalgia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Vertigo	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Hypertension	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Diabetes mellitus	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Renal failure acute	Unrelated/ Unrelated	Not recovered/ Not resolved	Hospitalization
		Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Sepsis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Staphylococcal infection	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Blood osmolarity decreased	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
[a] Event was considered to be injection/procedure related.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
PF-04523655 0.4 mg Group					
F/48	547	Fall	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization
		Lower limb fracture	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization
M/89	57	Hypoglycemia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/68	54	Pulmonary congestion	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
		Hypertension	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
PF-04523655 1 mg Group					
M/56	341	Gastroenteritis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/83	169	Coronary artery occlusion	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
		Renal failure	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
	222	Hyperglycemia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/38	269	Colitis ulcerative	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/59	349	Rib fracture	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
		Road traffic accident	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
M/63	112	Renal cancer	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization; important medical event
M/49	157	Cataract subcapsular	Unrelated/ Unrelated	Recovered/ Resolved	Important medical event
M/51	83	Cataract subcapsular	Unrelated/ Unrelated	Recovered/ Resolved	Important medical event
	112	Retinal detachment	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization; important medical event

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
PF-04523655 1 mg Group					
M/68	56	Blindness	Unrelated/ Unrelated[a]	Recovered/ Resolved	Important medical event
M/57	2	Skin ulcer	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
		Joint dislocation	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
		Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
	246	Osteomyelitis	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization; important medical event
		Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
		Streptococcal bacteremia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Sepsis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening; important medical event
		Impaired healing	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization; important medical event
		Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
	289	Gangrene	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization; life-threatening; important medical event
		Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
		Abscess limb	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
[a] Event was considered to be injection/procedure related.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
PF-04523655 1 mg Group					
F/66	170	Hypertension	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/61	507	Renal failure acute	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/71	26	Cerebrovascular accident	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization; important medical event
PF-04523655 3 mg Group					
M/65	16	Cerebrovascular accident	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/70	563	Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/72	109	Atrial fibrillation	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	221	Endophthalmitis	Unrelated/ Unrelated[a]	Recovered/ Resolved with sequelae	Important medical event
F/52	218	Acute myocardial infarction	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening
F/63	338	Road traffic accident	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	388	Subdural hematoma	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
F/49	7	Pneumonia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	7	Anemia	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization
	9	Cardiac failure congestive	Unrelated/ Unrelated	Not recovered/ Not resolved	Hospitalization
	174	Laryngeal cyst	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	277	Hypertension	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Pneumonia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/65	84	Ischemic cardiomyopathy	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
[a] Event was considered to be injection/procedure related.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
PF-04523655 3 mg Group					
F/69	88	Liver disorder	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	346	Hepatic encephalopathy	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	348	Blood creatinine increased	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/68	193	Ischemic stroke	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/57	157	Cataract	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	383	Diabetic foot	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/67	315	Pneumonia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/71	580	Mania	Unrelated/ Unrelated	Not recovered/ Not resolved	Hospitalization
M/67	79	Dyspnea	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
M/45	72	Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/58	169	Deafness neurosensory	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization
	439	Cardiac arrest	Unrelated/ Unrelated	Fatal	Fatal
M/67	469	Myocardial ischemia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; important medical event
M/54	432	Femur fracture	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
Laser Photocoagulation Group					
F/91	186	Chronic obstructive pulmonary disease	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	203	Syncope	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	762	Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	765	Renal failure acute	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Hyperkalemia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	794	Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Renal failure acute	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Cellulitis	Unrelated/ Unrelated	Recovering/ Resolving	Hospitalization
	832	Chronic obstructive pulmonary disease	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Pneumonia aspiration	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	867	Pneumonia aspiration	Unrelated/ Unrelated	Fatal	Hospitalization; life-threatening
F/75	103	Myocardial infarction	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
	151	Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
	465	Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening
	572	Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening
	579	Hypoglycemia	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening
F/62	190	Ischemic cardiomyopathy	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening
	201	Cardiac failure congestive	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization; life-threatening

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
F = female; MedDRA = Medical Dictionary for Regulatory Activities.

Table 9. Serious Adverse Events

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Sex/age (years)	Day of Onset	Preferred Term	Sponsor/ Investigator Relationship to Treatment	Outcome	Seriousness
Laser Photocoagulation Group					
M/77	88	Fall	Unrelated/ Unrelated	Unknown	Hospitalization
M/58	79	Blood creatine phosphokinase increased	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
		Blood creatinine increased	Unrelated/ Unrelated	Recovered/ Resolved with sequelae	Hospitalization
		Renal failure chronic	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/68	283	Coronary artery disease	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/71	79	Prostate cancer	Unrelated/ Unrelated	Recovered/ Resolved	Important medical event
M/52	450	Neuropathic ulcer	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Cellulitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
		Osteomyelitis	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/55	349	Localized infection	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/59	59	Post procedural infection	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization
M/69	150	Diabetic foot	Unrelated/ Unrelated	Recovered/ Resolved	Hospitalization

Age was at date of event onset. MedDRA (v13.1) coding dictionary was applied.
An additional 4 subjects reported SAEs prior to randomization (pancreatic tumor, hypertensive crisis, and apoplexy, flu, and hypertension).
M = male; MedDRA = Medical Dictionary for Regulatory Activities.

Changes from baseline in clinical laboratory results, vital signs, ECGs, biomicroscopy examination findings, IOP (except within 60 minutes of the IVT injection), refractive error, intraocular inflammation, and posterior lens capsule status were minimal and not clinically significant.

The incidence of AEs of hypertension appeared to have a positive association with PF-04523655 dose level, but when objective cutoffs were applied to the blood pressure (BP) measurements, all of the treatment groups look similar in terms of the incidence of hypertension.

CONCLUSIONS:

- The study was terminated on 17 December 2010 following the independent IARC's recommendation based on internal pre-determined futility criteria for efficacy and subject discontinuation. The trial was not discontinued for safety reasons. No subjects completed the 36-month study period.

- Prior to study termination, by Month 12 the discontinuation rates in the PF-04523655 groups were all substantially higher than the laser photocoagulation group and were inversely related to dose levels.

- All 3 dose levels of PF-04523655 continued to improve visual acuity from baseline through Month 12 in subjects with DME. At Month 12, the PF-04523655 3 mg group (5.77 letters) showed statistically significantly greater improvement in BCVA from baseline than the laser photocoagulation group (2.39 letters) ($p = 0.08$; 2-sided $\alpha = 0.10$).

- There were positive correlations between PF-04523655 dose level and BCVA change from baseline as well as proportion of subjects gaining ≥15 letters. The results from proportions of subjects who gained ≥10 letters or lost ≥15 letters, change from baseline in retinal central subfield thickness, macular volume, fluorescein leakage area and PROs did not show a dose response.

- Treatment with IVT PF-04523655 was generally safe and well-tolerated, with very few AEs that were considered to be treatment related, and the majority of AEs were mild or moderate in severity.

- No SAEs or deaths were considered to be treatment related.

- There were 2 cases of endophthalmitis in the PF-04523655 groups attributed to the injection procedure. In 1 of the subjects, the affected eye was eviscerated.

- Due to early study termination and high discontinuation rates in the PF-04523655 groups by Month 12, population-based dosing intervals in the PRN phase (post Month 6) could not be estimated without bias.

- Administration of PF-04523655 in doses up to 3 mg by the IVT route resulted in negligible systemic exposure.