Supplemental Material

METHODS

Study design and participants

A protocol amendment in 2010 allowed patients who had not yet completed the study and who met retreatment criteria to be retreated at month 36 with follow-up at month 39. Over 50% of patients had exited the study before this amendment was instituted.

Time-domain optical coherence tomography

Optical coherence tomography measures of interest were mean and average (area under the curve approach) changes from baseline in retinal thickness in the 1-mm central subfield and the change in macular volume, with both parameters measured from the internal limiting membrane to the inner/outer segment junction by the computer software. The reliability of optical coherence tomography readings was evaluated by graders; if artefacts were deemed to render the scan segmentation unreliable, manual calliper measurements of centre point thickness were used.

Stereoscopic colour fundus photography

Seven-field standard Early Treatment Diabetic Retinopathy Study (ETDRS) photographs were obtained at 6, 12, 24, 36 and 39 months, and three-field macular images at intervening timepoints. Fundus photographs of the study eye were assessed for presence and extent of retinal thickening, diabetic retinopathy severity level and presence of clinically significant macular oedema. Diabetic retinopathy was graded using the ETDRS Final Retinopathy Severity Scale condensed to nine severity categories: (1) diabetic retinopathy absent; (2) microaneurysms only; (3) mild nonproliferative diabetic retinopathy (NPDR); (4) moderate

NPDR; (5) moderately severe NPDR; (6) severe NPDR; (7) mild proliferative diabetic retinopathy (PDR); (8) high-risk PDR; or (9) advanced PDR. Clinically significant macular oedema was graded as: (1) none; (2) questionable; (3) retinal thickening ≥1 disc area, part ≤1 disc diameter from macula centre; or (4) retinal thickening or adjacent hard exudates ≤500 µm from macula centre.[1] Outcomes of interest included the change from baseline in disc area of central retinal thickening and the change from baseline in macular oedema grade (classified as improvement [shift from a higher grade to a lower grade], no change, or worsening [shift from a lower grade to a higher grade]).

Fluorescein angiography

Transit images were taken of the study eye and mid- and late-phase images were taken of both eyes. Angiographic assessments focused on the presence and extent of fluorescein leakage (expressed as Macular Photocoagulation Study disc areas within the ETDRS macular grid) and area of macular capillary loss (non-perfusion). Grading protocols were adapted from the ETDRS clinical trials and were designed to provide qualitative and semiquantitative (ie, non-planimetric) assessments of angiographic endpoints.[2] The mean change from baseline to study end in total disc area of macular capillary loss and the proportions of patients with and without ischaemia (defined as a total area of capillary loss >0.5 disc area) at baseline and the last visit were determined.

RESULTS

Study population

The lower completion rate in the sham group largely resulted from discontinuations due to lack of efficacy (n=84), which were >3-fold more frequent than in the DEX implant 0.7 mg

(n=23) and 0.35 mg (n=25) groups. Discontinuations due to adverse events, reported previously, were similar among all groups (DEX implant 0.7 mg, n=28 ocular, n=17 non-ocular; DEX implant 0.35 mg, n=28 ocular, n=20 non-ocular; sham, n=27 ocular, n=12 non-ocular).[3] Sample sizes and statistical power were not reduced because of patient discontinuations.

Fundus photography findings – reproducibility

Assessment of grading reproducibility for the extent of central retinal thickening yielded a weighted kappa of 0.63. Quality control measurement of area of retinal thickening resulted in an intra-class correlation (ICC) of 0.87, with 78% of measurements within two disc areas. The reproducibility of ETDRS diabetic retinopathy severity grading yielded a weighted kappa of 0.81 (95% confidence interval 0.77–0.84).

Fluorescein angiography findings – reproducibility

Assessment of grading reproducibility for measurement of fluorescein leakage area yielded an ICC of 0.959, with 63% of measurements within one disc area, and the reproducibility for the area of capillary loss demonstrated an ICC of 0.935, with 91% of measurements within one disc area.

REFERENCES

1. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98(5 Suppl):786–806.

2. Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98(5 Suppl):807–22.

3. Boyer DS, Yoon YH, Belfort R, Jr., et al.; for the Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014;121:1904–14 doi: 10.1016/j.ophtha.2014.04.024 [Published Online First: 4 June 2014].

Supplemental Table 1. Mean change from baseline in retinal thickness in the central subfield at all study time points for dexamethasone intravitreal implants and sham procedure

Time (months)	**Mean (SD) change from baseline in retinal thickness in the central subfield (μm)**		
	DEX implant 0.7 mg (N=348)	**DEX implant 0.35 mg (N=344)**	**Sham procedure (N=342)**
3	−158.2 (165.0)	−148.5 (168.6)	−17.4 (112.3)
6	−63.9 (152.4)	−49.6 (149.3)	−24.6 (122.8)
9	−150.3 (180.4)	−142.4 (181.2)	−30.7 (145.1)
12	−78.0 (174.5)	−74.3 (178.3)	−33.1 (153.0)
15	−142.6 (189.9)	−137.4 (185.9)	−34.6 (159.1)
18	−84.3 (183.8)	−97.4 (186.4)	−46.0 (162.5)
21	−130.2 (200.8)	−128.9 (201.5)	−51.2 (164.5)
24	−100.1 (208.1)	−106.9 (191.4)	−58.0 (170.0)
27	−108.6 (209.4)	−124.4 (201.1)	−55.4 (173.1)
30	−100.3 (207.8)	−104.2 (189.9)	−61.2 (180.6)
33	−111.0 (211.8)	−124.0 (196.1)	−63.5 (177.6)
36	−103.1 (206.5)	−112.2 (193.9)	−62.0 (177.2)
39/Final visit	−117.3 (208.1)	−127.8 (196.6)	−62.1 (180.1)

DEX implant, dexamethasone intravitreal implant; SD, standard deviation

Supplemental Table 2. Cumulative treatment exposure in the safety population

Time (months)	**DEX implant 0.7 mg N (%)**	**DEX implant 0.35 mg N (%)**	**Sham procedure N (%)**
Baseline	347 (100.0)	343 (100.0)	350 (100.0)
3	343 (98.8)	342 (99.7)	331 (94.6)
6	339 (97.7)	335 (97.7)	304 (86.9)
9	320 (92.2)	325 (94.8)	266 (76.0)
12	304 (87.6)	314 (91.5)	242 (69.1)
15	286 (82.4)	302 (88.0)	218 (62.3)
18	278 (80.1)	295 (86.0)	199 (56.9)
21	268 (77.2)	279 (81.3)	186 (53.1)
24	261 (75.2)	269 (78.4)	176 (50.3)
27	250 (72.0)	261 (76.1)	171 (48.9)
30	242 (69.7)	253 (73.8)	164 (46.9)
33	234 (67.4)	245 (71.4)	161 (46.0)
36	139 (40.1)	145 (42.3)	93 (26.6)
39	18 (5.2)	16 (4.7)	11 (3.1)

DEX implant, dexamethasone intravitreal implant