OZDRY Final Analysis

Prepared by Ana Quartilho and Catey Bunce

For all effect estimates presented, the reference group is PRN (control arm).

Table 1: Non-Ocular Baseline Characteristics by Study Arm (of study patient)

	Fixed dosing (N=50)	**PRN dosing (N=50)**
Number of patients (eyes), n	50	50
Males, n (%) [N]	40 (80) [50]	34 (68) [50]
Age (years), mean (SD) [N]	63.8 (11.1) [50]	65.4 (9.8) [50]
Ethnicity [N] White / Caucasioan, n (%) Black or African, n (%) Sout Asian, n (%) Other, n (%)	[50] 34 (68) 5 (10) 10 (20) 1 (2)	[50] 35 (70) 5 (10) 8 (16) 2 (4)
Diabetes [N] Type 1, n (%) Type 2 on insulin, n (%) Type 2 on tablets, n (%)	[50] 7 (14) 22 (44) 21 (42)	[50] 2 (4) 22 (44) 26 (52)
Duration of DM (months) median (IQR) [N]	192 (112, 255) [50]	196 (124, 249) [50]
HbA1c (%), mean (SD) [N]	8.1 (1.4) [50]	7.7 (1.3) [50]
Systolic BP (mmHg), mean (SD) [N]	148.5 (20.5) [50]	142.8 (20.5) [50]
Diastolic BP (mmHg), mean (SD) [N]	79.3 (9.8) [50]	77.7 (10.8) [50]
Study site [N] Moorfields, n (%) Wolverhampton, n (%) Bristol, n (%) Frimley, n (%) Brighton, n (%)	[50] 16 (32) 13 (26) 4 (8) 13 (26) 4 (8)	[50] 16 (32) 12 (24) 6 (12) 12 (24) 4 (8)

BP = blood pressure; DM = diabetes mellitus; n = number of patients (eyes); N = total number of patients (eyes); SD = standard deviation; IQR = interquartile range

Table 2: Ocular Baseline Characteristics by Study Arm (of study eye)

	Fixed dosing (N=50)	**PRN dosing (N=50)**
Laterality: right, n (%) [N]	27 (54) [50]	27 (54) [50]
ETDRS BCVA, mean (SD) [N]	57.5 (9.5) [50]	61.2 (8.6) [50]
VA group [N] <54 ETDRS letters, n (%) ≥54 ETDRS letters, n (%)	[50] 15 (30) 35 (70)	[50] 9 (18) 41 (82)
Duration of CSMO (months), median (IQR) [N]	35.5 (15.0, 51.0) [50]	37.0 (18.0, 48.0) [50]
Prior MLTs, n (%) [N] Number of prior MLTs, median (IQR) [N] MLT within last 12 months, n (%) [N]	46 (96) [48] 2 (1, 3) [45] 18 (39) [46]	48 (96) [50] 2 (1, 3) [48] 20 (42) [48]
Prior PRP, n (%) [N] PRP within last 12 months, n (%) [N]	14 (28) [50] 5 (36) [14]	8 (16) [50] 2 (25) [8]
CRT (µm), mean (SD) [N] CST (µm), mean (SD) [N] Macular volume (mm^3), mean (SD) [N]	479.8 (128.4) [50] 472.4 (113.5) [50] 10.0 (2.5) [50]	466.7 (144.1) [50] 467.9 (126.4) [50] 10.4 (2.1) [50]
Morphology of macular oedema: Intraretinal diffuse oedema, n (%) [N] Intraretinal cysts, n (%) [N] Subretinal fluid, n (%) [N] Area of hypoautoflurescence (μm^2), median (IQR) [N] Area of hyperautofluorescence (μm^2), median (IQR) [N] Hard exudates in central 6mm fovea, n (%) [N]	 43 (83) [50] 48 (96) [50] 9 (18) [50] 0.3 (0.2, 0.6) [14] 0.4 (0.2, 0.7) [29] 21 (42) [50]	 41 (82) [50] 50 (100) [50 13 (26) [50]] 0.2 (0.1, 0.6) [19] 0.5 (0.2, 0.6) [27] 34 (68) [50]
Type of lens [N] Pseudophakic, n (%) Phakic, n (%)	 16 (32) [50] 34 (68) [50]	 11 (22) [50] 39 (78) [50]
Previous treatment for glaucoma, n (%) [N]	0 (0) [50]	1 (2) [50]
Prior cataract, n (%) [N]	8 (16) [50]	13 (26) [50]
ETDRS grade of retinopathy [N] Mild NPDR, n (%) Moderate NPDR, n (%) Severe NPDR, n (%) Treated PDR, n (%)	[49] 16 (33) 17 (35) 5 (10) 11 (22)	[50] 17 (34) 21 (42) 7 (14) 5 (10)
FAZ GLD (mm), mean (SD) [N]	808.5 (271.8) [50]	769.0 (190.4) [50]
FAZ Area (mm^2), median (IQR) [N]	0.5 (0.3, 0.7) [49]	0.4 (0.3, 0.6) [50]

ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; VA = visual acuity; CSMO = clinically significant macular oedema; MLT = macular laser therapy; CRT = central retinal thickness; CST = central subfield thickness; NPDR = mild non-proliferative diabetic retinopathy (NPDR); PDR = proliferative diabetic retinopathy; FAZ – foveal avascular zone; GLD = greatest linear dimension; n = number of patients (eyes); N = total number of patients (eyes); SD = standard deviation; IQR = interquartile range; PRP=pan retinal photocoagulation

Please note that for the primary outcome we are assessing non-inferiority and therefore the lower limit of a one-sided 95% CI is derived from a two-sided 90% CI (both have the same lower limit).

Although one-sided p-values are provided, presentation of results should focus on the effect estimate and respective confidence interval.

For a non-inferiority margin of 5 ETDRS letters, the null hypothesis is that, Fixed is inferior to PRN and the alternative hypothesis is that Fixed is non-inferior to PRN.

For interpretation purposes, if the lower limit of the 90% CI contains -5 then there is no evidence to reject the null hypothesis. Conversely, if the 90% CI does not contain -5 then there is evidence to reject the null hypothesis.

Missing data were below the 10% as per approved SAP and thus primary intention to treat (ITT) analysis effect estimates are based on available cases (12 months data is not available for 3 patients who withdrew/died).

Table below summaries the primary outcome analyses for ITT and per protocol (PP) analyses and respective sensitivity analysis as per approved SAP. Also presented are the results of a post hoc ITT analysis using last observation carried forward (LOCF) for the 3 patients with missing 12 months primary outcome data.

For the PP analysis, the confidence interval does not contain -5 and thus we reject the null hypothesis (overall 5 patients excluded – 1 Fixed, 2 PRN withdrew/died; 1 PRN, 1 Fixed due to AE).

Table 3: Primary Analyses by Study Arm – Efficacy outcome measures

	Fixed dosing (N=50)	**PRN dosing (N=50)**	**Effect Estimate (two-sided 90% CI)**	**One-sided P-value**
Intention To Treat (ITT) Analysis (available case)				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	57.8 (18.5) [49]	61.4 (14.0) [48]	-	-
- Change from baseline*	0.53 (16.1) [49]	0 (13.0) [48]	-0.34 (-5.49, 4.81)	0.07
Per Protocol (PP) Analysis				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	58.5 (17.9) [48]	61.1 (14.0) [47]	-	-
- Change from baseline*	1.48 (14.8) [48]	-0.17 (13.1) [47]	0.97 (-4.01, 5.95)	0.02

Post Hoc Last Observation Carried Forward (LOCF) ITT Analysis				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	58.0 (18.4) [50]	60.8 (14.2) [50]	-	-
- Change from baseline*	0.52 (15.9) [50]	-0.44 (13.0) [50]	0.28 (-4.72, 5.27)	0.04
Intention To Treat (ITT) Sensitivity Analysis (available case): Cataract Surgery				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	57.6 (18.6) [49]	59.8 (14.1) [48]	-	-
- Change from baseline*	0.35 (16.0) [49]	-1.65 (13.2) [48]	1.18 (-3.97, 6.34)	0.02
Intention To Treat (ITT) Sensitivity Analysis (available case): Pseudophakic at Baseline				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	58.3 (19.9) [15]	63.2 (14.5) [10]	-	-
- Change from baseline*	0.53 (14.7) [15]	1.2 (13.6) [10]	0.73 (-11.4, 12.9)	0.2
Per Protocol (PP) Sensitivity Analysis: Cataract Surgery				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	58.3 (18.0) [48]	59.4 (14.0) [47]		-
- Change from baseline*	1.29 (14.7) [48]	-1.85 (13.2) [47]	2.51 (-2.48, 7.50)	0.007
Per Protocol (PP) Sensitivity Analysis: Pseudophakic at Baseline				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	61 (17.7) [14]	63.2 (14.5) [10]		-
- Change from baseline*	3.78 (7.8) [14]	1.2 (13.6) [10]	5.81 (-2.44, 14.05)	0.02
Post Hoc LOCF ITT Sensitivity Analysis: Cataract Surgery				
ETDRS BCVA, mean (SD) [N]				
- At 12 months	57.8 (18.5) [50]	59.2 (14.2) [50]	-	-
- Change from baseline*	0.34 (15.8) [50]	-2.02 (13.1) [50]	1.73 (-3.26, 6.72)	0.01
Post Hoc LOCF ITT Sensitivity Analysis: Pseudophakic at Baseline				
ETDRS BCVA, mean (SD) [N]				

- At 12 months	59.1 (19.5) [16]	61.9 (14.4) [11]	-	-
- Change from baseline*	0.5 (14.2) [16]	0.64 (13.1) [11]	1.22 (-9.51, 11.96)	0.16

ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; N = total number of patients (eyes)

* Adjusted for baseline BCVA and study site

Table 4: Secondary Analyses by Study Arm – Efficacy outcome measures

	Fixed dosing (N=50)	PRN dosing (N=50)	Effect Estimate (95% CI)
Proportion of patients with improvement in BCVA at 12 months from baseline (gaining ≥10 ETDRS letters)*, n (%) [N]	12 (24) [49]	11 (23) [48]	0.82 (0.3, 2.3)
Proportion of patients with stabilisation in BCVA at 12 months from baseline (losing <15 ETDRS letters)*, n (%) [N]	42 (86) [49]	44 (92) [48]	0.56 (0.15, 2.18)
Distribution of change in BCVA at 12 months from baseline* [N]	[49]	[48]	Odds ratio for each
≥15 letters improvement, n (%)	7 (14)	4 (8)	1.3 (0.33, 5.40)
≥5 and <15 letters improvement, n (%)	14 (29)	12 (25)	1.3 (0.50, 3.36)
≥4 and <5 letters (i.e. no change), n (%)	4 (8)	2 (4)	2.5 (0.40, 15.62)
≥5 and <15 letters worsening, n (%)	4 (8)	7 (15)	0.65 (0.17, 2.60
≥15 letters worsening, n (%)	7 (14)	4 (8)	1.76 (0.46, 6.76)
CST, mean (SD) [N]			
- At 12 months	292.9 (118.9) [47]	372.3 (117.3) [47]	-
- Change from baseline*	-179.9 (172.4) [47]	-90.1 (96.2) [47]	-71.34 (-117.33, -25,34)
Change in 12 month ETDRS grade of retinopathy from baseline* [N]	[46]	[45]	
-2, n (%)	1 (2)	0 (0)	-
-1, n (%)	1 (2)	9 (20)	
0, n (%)	38 (83)	29 (64)	
1, n (%)	4 (9)	4 (9)	
2, n (%)	2 (4)	3 (7)	
3, n (%)	0 (0)	0 (0)	
4, n (%)	0 (0)	0 (0)	
Number of treatments per patient, mean (SD) / median (IQR) [N]	2.86 (0.45) / 3 (3, 3) [50]	2.60 (0.70) / 3 (2, 3) [50]	0.26 (0.03, 0.49)
Change in morphology of macular oedema from baseline*:			
Intraretinal diffuse oedema, n (%) [N]	15 (31) [48]	25 (53) [47]	0.29 (0.11, 0.81)
Intraretinal cysts, n (%) [N]	36 (75) [48]	39 (83) [47]	0.67 (0.23,

			1.95)
Subretinal fluid, n (%) [N]	0 (0) [47]	3 (6) [47]	-
Change in Area of hypoautoflurescence (μm^2), median (IQR) [N]	-0.04 (-0.13, -0.02) [5]	-0.19 (-0.22, -0.19) [5]	-
Change in Area of hyperautofluorescence (μm^2), median (IQR) [N]	-0.2, (-0.4, -0.1) [13]	-0.09 (-0.48, 0.02) [14]	-
Hard exudates in central 6mm fovea, n (%) [N]	18 (38) [47]	28 (62) [45]	0.59 (0.21, 1.67)

* Adjusted for baseline BCVA, study site and respective baseline covariate

Table 5: Secondary Analyses by Study Arm – Safety outcome measures

	Fixed dosing (N=50)	PRN dosing (N=50)	Effect Estimate (95% CI)
FAZ GLD (um), mean (SD) [N]			
- At 12-months	931.1 (366.3) [42]	824.5 (272.1) [45]	
- Change from baseline*	152.8 (419.2) [42]	55.4 (293.8) [45]	108.2 (-16.4, 232.7)
FAZ Area (mm^2)*, median (IQR) [N]			
- At 12-months	0.47 (0.31, 0.78) [41]	04 (0.27, 0.56) [45]	
- Change from baseline*	0.03 (-0.11, 0.3) [41]	-0.05 (-0.14, 0.16) [45]	0.06 (-0.11, 0.23)
Systolic BP (mmHg) at 12 months, mean (SD) [N]			
- At 12-months	139.9 (18.2) [49]	140.9 (16.1) [48]	
- Change from baseline*	-8.1 (22.5) [49]	-2.5 (21.5) [48]	-2.98 (-9.60, 3.63)
Diastolic BP (mmHg), mean (SD) [N]			
- At 12-months	75.5 (9.5) [49]	76.6 (10.2) [48]	
- Change from baseline*	-3.8 (10.4) [49]	-1.5 (8.6) [48]	-1.95 (-5.43, 1.53)
HbA1c (%), mean (SD) [N]			
- At 12-months	8.1 (1.6) [49]	7.8 (1.54) [48]	
- Change from baseline*	-0.001 (1.41) [49]	0.12 (1.45) [48]	-0.02 (-0.56, 0.53)
Cataract surgery in study eye during 12 months, n (%) [N]	1 (0) [49]	4 (8.3) [48]	-
Commenced topical treatment for glaucoma, n (%) [N]			-
Required laser/surgical intervention for glaucoma, n (%) [N]			-

BP = blood pressure; FAZ = foveal avascular zone; GLD = greatest linear dimension; IQR = interquartile range; PFCL = perifoveal capillary loss

* Adjusted for baseline BCVA, study site and respective baseline covariate

Table 6: Secondary Analyses by Study Arm – Patient reported outcome measures

	Fixed dosing (N=50)	PRN dosing (N=50)	Effect Estimate (95% CI)
Change composite scores of the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25)*	3.02 (15.4) [49]	-0.45 (12.2) [47]	3.1 (-2.1, 8.3)
Change in each domain score:			
- General Health*	1.56 (25.0) [48]	-4.79 (22.5) [47]	0.6 (-7.4, 8.6)
- General Vision*	2.04 (17.0) [49]	2.13 (17.8) [47]	1.0 (-5.8, 7.8)
- Ocular Pain*	2.04 (19.5) [49]	-5.32 (19.3) [47]	5.7 (-1.3, 12.8)
- Near Activities*	3.15 (23.3) [49]	-2.22 (17.1) [47]	5.8 (-1.4, 13.1)
- Distance Activities*	2.04 (19.5) [49]	-5.32 (19.3) [47]	5.7 (-1.3, 12.8)
- Social Functioning*	6.12 (20.9) [49]	-2.13 (18.5) [47]	6.3 (-0.6, 13.3)
- Mental Health*	4.46 (26.4) [49]	6.38 (21.5) [47]	-1.1 (-10.2, 8.0)
- Role Difficulties*	-1.27 (29.7) [49]	0.27 (25.3) [47]	1.7 (-8.3, 11.6)
- Dependency*	1.36	2.72	-1.3 (-11,

	(27.0) [49]	(23.8) [46]	8.5)
- Driving*	0.93 (5.8) [27]	1.52 (13.1) [33]	-1.4 (-7.5, 4.7)
- Color Vision*	7.65 (25.6) [49]	-1.63 (8.2) [46]	2.7 (-3.5, 8.9)
- Peripheral Vision*	4.17 (27.9) [48]	-3.26 (27.7) [46]	4.8 (-4.1, 13.7)
Retinopathy Treatment Satisfaction Questionnaire (RetTSQ)*	4.4 (12.7) [49]	3.6 (15.1) [47]	2.7 (-2.3, 7.7)
Retinopathy-Dependent Quality of Life questionnaire (RetDQoL)*	-0.38 (1.7) [49]	-0.14 (1.6) [48]	-0.16 (-0.8, 0.5)

* Adjusted for baseline BCVA, study site and respective baseline covariate