Supplementary

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SUPPLEMENTARY TABLE 1: Baseline Data

	Group L1 (n = 204)	Group S1 (n = 203)	Group L2 (n = 203)	Group S2 (n =202)	Total (n =812)
Age at enrolment (years):					
mean [SD]	79 [7.5]	80 [7.6]	80 [7.4]	81 [7.0]	80 [7.4]
Min, max	54, 95	54, 98	60, 99	62, 101	54, 101
Gender					
Male	84 (41)	85 (42)	85 (42)	93 (46)	347 (43)
Female	120 (59)	118 (58)	118 (58)	109 (54)	465 (57)
Smoking history					
Current smoker	29 (14)	27 (13)	21 (10)	25 (12)	102 (13)
Ex-smoker	108 (53)	104 (51)	103 (51)	103 (51)	418 (51)
Never smoked	67 (33)	72 (35)	79 (39)	74 (37)	292 (36)
Neovascular lesion involving the centre of fovea					
Primary eye	173 (85)	179 (88)	183 (90)	175 (87)	710 (87)
Fellow eye (n=105)	29 (88)	21 (84)	18 (82)	22 (85)	90 (85)
GLD >6000 um					
Primary eye	0	4 (2)	6 (3)	3 (1)	13 (2)
Fellow eye	2 (6)	2 (8)	0	0	4 (4)
Long standing CNV Fibrosis > 50%					
Primary eye	3 (1)	3 (1)	3 (1)	4 (2)	13 (2)
Fellow eye	1 (3)	1 (4)	0	0	2 (2)
Thick blood involving centre of fovea					
Primary eye	2 (1)	3 (1)	4 (2)	4 (2)	13 (2)
Fellow eye	0	0	0	0	0
Refraction > - 6DS (primary eye)					
Yes	2 (1)	1 (<0.5)	2 (1)	0	5 (1)
No	202 (99)	202 (99)	200 (99)	202 (100)	803 (99)
Missing	0	0	1 (<0.5)	0	1 (<0.5)
Considered primary eye					
Right	104 (51)	108 (53)	95 (47)	101 (50)	408 (50)
Left	100 (49)	95 (47)	108 (53)	101 (50)	404 (50)
Medical history					
Heart failure	18 (9)	15 (7)	15 (7)	12 (6)	60 (7)
Myocardial	20 (10)	20 (10)	17 (8)	14 (7)	71 (9)
History of angina	21 (10)	36 (18)	23 (11)	28 (14)	108 (13)
Any ocular history other than spectacles					
Yes	81 (40)	83 (41)	89 (44)	88 (44)	341 (42)
No	123 (60)	120 (59)	114 (56)	114 (56)	471 (58)
Current medication					
Diuretic	69 (34)	57 (28)	61 (30)	53 (26)	240 (30)
Beta-blocker	44 (22)	47 (23)	48 (24)	44 (22)	183 (23)
Statin	93 (46)	105 (52)	84 (41)	94 (47)	376 (46)
Anticoagulant	26 (13)	20 (10)	18 (9)	15 (7)	79 (10)
Aspirin	47 (23)	64 (32)	48 (24)	62 (31)	221 (27)
Ace inhibitors	50 (25)	61 (30)	59 (29)	54 (27)	224 (28)
Other anti-platelet therapy	8 (4)	8 (4)	8 (4)	6 (3)	30 (4)
Visual acuity~~A~~ at baseline (visit A)					
Primary eye mean(sd)	56.1 (15.1)	56.2 (14.0)	56.7 (13.3)	56.0 (13.9)	56.3 (14.1)
Median (IQR)	60 (48, 67)	59 (50, 67)	60 (49, 67)	59 (48, 67)	59 (48, 67)
min, max	20, 83	8, 80	25, 89	16, 78	8, 89
n	200	199	201	199	799
Fellow eye mean (sd)	60.0 (12.7)	59.1 (14.9)	62.0 (12.2)	62.0 (10.1)	60.9 (12.5)
Median (IQR)	64.5 (56, 67.5)	63 (50, 69)	62 (53, 72)	62.5 (57, 69)	63 (55, 69)
min. max	27, 85	21, 79	36, 83	28, 78	21, 85
n	32	25	22	26	105
Primary Eye Distance visual acuity[†]:					
mean [SD]	58.7 [15.9]	58.3 [14.4]	59.4 [12.8]	58.3 [14.3]	58.7 [14.4]
median (IQR)	64 [49.5, 70]	60 [51, 70]	62 [50, 69]	63 [50, 70]	63 [50, 70]
Min, max	14, 83	14, 83	23, 86	18, 81	9, 86
n	200	199	201	199	799
Fellow Eye Distance visual acuity[†]:					
mean [SD]	62.3 [13.6]	60.8 [15.5]	64.1 [12.0]	64.9 [10.7]	63.0 [13.0]
median (IQR)	64.5 [57.5, 72.5]	65 [52, 72]	65 [55, 76]	68.5 [59, 71]	66 [58, 71]
Min, max	30, 84	25, 82	32, 82	27, 82	25, 84
n	32	25	22	26	105
Patients visual acuity dropped >=15 letters at visit B[‡]	1 (<0.5)	4 (2)	0	3 (8)	8 (1)

	Group L1 (n = 204)	Group S1 (n = 203)	Group L2 (n = 203)	Group S2 (n =202)	Total (n =812)
Patients visual acuity dropped >=15 letters at visit C‡	1 (<0.5)	4 (2)	0	1 (<0.5)	6 (1)
CV size (area)					
Primary eye mean(sd)	2.4 (2.9)	2.5 (3.3)	2.4 (3.2)	2.2 (3.5)	2.4 (3.2)
Median (IQR)	1.3 (0.5, 3.1)	1.6 (0.7, 3.3)	1.4 (0.6,2.6)	1.0 (0.6, 2.3)	1.4 (0.6,3.0)
min, max	0.01. 15.6	0.07. 25.2	0.03. 20.3	0.07. 20.8	0.01. 25.2
n	94	72	77	75	318
<=4	78 (38)	58 (29)	65 (32)	66 (33)	267 (33)
>4	16 (8)	14 (7)	12 (6)	9 (4)	51 (6)
Missing	110 (54)	131 (65)	126 (62)	127 (63)	494 (61)
Fellow eye mean (sd)	0.1 (0.2)	6.8 (6.9)	1.5 (0.07)	2.5 (2.9)	2.9 (4.3)
Median (IQR)	0.06 (0.02,0.25)	5.6 (1.2,12.5)	1.5 (1.4,1.5)	1.2 (1.0,3.2)	1.2 (0.5,2.4)
Min, max	0.02, 0.4	0.8, 15.3	1.4, 1.5	0.5, 8.2	0.02, 15.3
n	4	4	2	6	16
<=4	4 (12)	2 (8)	2 (9)	5 (19)	13 (12)
>4	0 (0)	2 (8)	0 (0)	1 (4)	3 (3)
Missing	29 (88)	21 (84)	20 (91)	20 (77)	90 (85)
Lesion composition					
Primary eye Classic CNV: No	91 (45)	104 (51)	99 (49)	103 (51)	397 (49)
Yes	94 (46)	72 (35)	77 (38)	75 (37)	318 (39)
Missing	19 (9)	27 (13)	27 (13)	24 (12)	97 (12)
Occult: No	55 (27)	51 (25)	49 (24)	46 (23)	201 (25)
Yes	132 (65)	125 (62)	128 (63)	131 (65)	516 (64)
Missing	17 (8)	27 (13)	26 (13)	25 (12)	95 (12)
Classic CNV, no occult	55 (37)	51 (25)	48 (24)	46 (23)	200 (25)
Classic CNV and occult	39 (19)	19 (9)	29 (14)	27 (13)	114 (14)
No classic CNV, occult	91 (45)	104 (51)	98 (48)	103 (51)	396 (49)
Missing	19 (9)	29 (14)	28 (14)	26 (13)	102 (13)
Fellow eye Classic CNV: No	9 (27)	7 (28)	9 (41)	8 (31)	33 (31)
Yes	4 (12)	4 (16)	2 (9)	6 (23)	16 (15)
Missing	20 (61)	14 (56)	11 (50)	12 (46)	57 (54)
Occult: No	2 (6)	2 (8)	1 (5)	5 (19)	10 (9)
Yes	11 (33)	9 (36)	10 (45)	9 (35)	39 (37)
Missing	20 (61)	12 (46)	11 (50)	12 (46)	57 (54)
Classic CNV, no occult	2 (6)	2 (8)	1 (5)	5 (19)	10 (9)
Classic CNV and occult	2 (6)	2 (8)	1 (5)	1 (4)	6 (6)
No classic CNV, occult	9 (27)	7 (28)	9 (41)	8 (31)	33 (31)
Missing	20 (61)	14 (56)	11 (50)	12 (46)	57 (54)
Lesion subtype					
Primary eye: Classic CNV	55 (27)	53 (26)	48 (24)	48 (24)	204 (25)
FPED	108 (53)	106 (52)	107 (53)	108 (54)	429 (53)
SPED	12 (6)	6 (3)	8 (4)	13 (6)	39 (5)
LLIO	2 (1)	1 (0.5)	0 (0)	0 (0)	3 (<0.5)
RAP	10 (5)	12 (6)	13 (6)	10 (5)	45 (5)
Missing	17 (8)	25 (12)	27 (13)	23 (11)	92 (11)
Fellow eye: Classic CNV	2 (6)	2 (8)	1 (5)	5 (19)	10 (9)
FPED	9 (27)	7 (28)	10 (45)	7 (27)	33 (31)
SPED	0 (0)	0 (0)	0 (0)	1 (4)	1 (1)
LLIO	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RAP	2 (6)	2 (8)	0 (0)	1 (4)	5 (5)
Missing	20 (61)	14 (56)	11 (50)	12 (46)	57 (54)
Structural damage					
Primary eye No	145 (71)	142 (70)	148 (73)	148 (73)	583 (72)
Yes	43 (21)	42 (21)	30 (15)	35 (17)	150 (18)
Missing	16 (8)	19 (9)	25 (12)	19 (9)	79 (10)
Fellow eye No	9 (27)	9 (36)	6 (27)	12 (46)	36 (34)
Yes	6 (18)	2 (8)	5 (23)	2 (8)	15 (14)
Missing	18 (55)	14 (56)	11 (50)	12 (46)	55 (52)

	Group L1 (n = 204)	Group S1 (n = 203)	Group L2 (n = 203)	Group S2 (n =202)	Total (n =812)
Disease activity					
Primary eye No	**20 (10)**	**23 (11)**	**19 (9)**	**22 (11)**	**84 (10)**
Yes	**169 (83)**	**160 (79)**	**156 (77)**	**157 (78)**	**642 (79)**
Missing	**15 (7)**	**20 (10)**	**28 (14)**	**23 (11)**	**86 (11)**
Fellow eye No	**1 (3)**	**1 (4)**	**0 (0)**	**3 (12)**	**5 (5)**
Yes	**13 (39)**	**9 (36)**	**11 (50)**	**11 (42)**	**44 (42)**
Missing	**19 (58)**	**15 (60)**	**11 (50)**	**12 (46)**	**57 (54)**
Diagnosis of CNV					
Primary eye No	**5 (2)**	**7 (3)**	**3 (1)**	**5 (2)**	**20 (2)**
Yes	**185 (91)**	**177 (87)**	**176 (87)**	**178 (88)**	**716 (88)**
Missing	**14 (7)**	**19 (9)**	**24 (12)**	**19 (9)**	**76 (9)**
Fellow eye No	**2 (6)**	**0 (0)**	**0 (0)**	**0 (0)**	**2 (2)**
Yes	**13 (39)**	**11 (44)**	**11 (50)**	**14 (54)**	**49 (46)**
Missing	**18 (55)**	**14 (56)**	**11 (50)**	**12 (46)**	**55 (52)**

*All data are n (%) unless otherwise indicated.

†mean of visual acuity at loading dose visit A, B and C

‡ Number of participants included in the table that satisfy the criteria, but did not exit when reaching event = four (due to different criteria in earlier version of protocol - changed 22 Sept 2011); two at visit B and two at visit C.

Treatment key: L1 = low dose, once a month schedule; S1 = standard dose, once a month schedule; L2 = low dose, bi-monthly schedule; S2 = standard dose, bi-monthly schedule

SUPPLEMENTARY TABLE 2: Total number of injections per primary eye, time in trial, and between visit duration

	Group L1 (n = 204)	**Group S1 (n = 203)**	**Group L2 (n =203)**	**Group S2 (n =202)**	**Total (n =812)**
Number of Injections*					
Mean (SD)	8.6 (6.7)	8.9 (7.6)	7.0 (4.5)	6.8 (4.9)	7.8 (6.1)
Median (IQR)	6 (4, 11)	6 (4, 12)	6 (4, 9)	5 (3, 8)	6 (4, 10)
Min, max	1, 37	1, 47	2, 29	1, 33	1, 47
Time in trial (months)					
Mean (SD)	47.6 (29.5)	50.2 (35.8)	45.4 (29.5)	48.2 (32.4)	47.9 (31.9)
Median (IQR)	38.2 (24.3, 68.8)	38.5(22.2, 75.3)	36.2 (24.2, 62.3)	40 (23.9, 66.8)	38.2 (23.3, 68.0)
Min, max	0.1, 133.4	2.3, 165.7	8.9, 164.5	0.1, 172.7	0.1, 172.7
Time between visits (days)					
Mean (SD)	35.9 (5.5)	35.5 (4.2)	52.6 (6.9)	53.5 (7.4)	44.4 (10.6)
Median (IQR)	35.2 (33.5, 38.3)	35 (33.1, 37.6)	53.7 (49, 57.8)	53.9 (50, 58)	42 (35, 53.9)
Min, max	23.3, 87.5	17.5, 54.4	28, 79.3	28, 77	17.5, 87.5
n	199	200	201	200	800

*** All participants should receive three loading doses, before the maintenance phase**

Treatment key: L1 = low dose, once a month schedule; S1 = standard dose, once a month schedule; L2 = low dose, bi-monthly schedule; S2 = standard dose, bi-monthly schedule

SUPPLEMENTARY TABLE 3: Adverse Events and Serious Adverse Events

	Group L1 (n=204)	Group S1 (n=203)	Group L2 (n=203)	Group S2 (n=202)
Number of participants reporting adverse event from first dose of trial treatment – 10 most frequent				
Event category (preferred term)	No. (%)	No. (%)	No. (%)	No. (%)
Fall	**35 (17.2)**	**43 (21.2)**	**28 (13.8)**	**29 (14.4)**
Lower respiratory tract infection	**28 (13.7)**	**25 (12)**	**27 (13.3)**	**26 (12.9)**
Injection site reaction[†]	**20 (9.8)**	**24 (11.8)**	**12 (5.9)**	**12 (5.9)**
Visual acuity reduced[†]	**23 (11.3)**	**18 (8.9)**	**13 (6.4)**	**13 (6.4)**
Conjunctival haemorrhage[†]	**18 (8.8)**	**17 (8.4)**	**12 (5.9)**	**10 (5.0)**
Eye pain[†]	**12 (5.9)**	**13 (6.4)**	**13 (6.4)**	**10 (5.0)**
Urinary tract infection	**12 (5.9)**	**16 (7.9)**	**10 (4.9)**	**10 (5.0)**
Headache	**9 (4.4)**	**20 (9.9)**	**11 (5.4)**	**8 (4.0)**
Dizziness	**8 (3.9)**	**15 (7.4)**	**10 (4.9)**	**11 (5.4)**
Nasopharyngitis	**11 (5.4)**	**15 (7.4)**	**9 (4.4)**	**5 (2.5)**
Number of adverse events from first dose of trial treatment – 10 most frequent[‡]				
Fall	**56**	**66**	**34**	**53**
Lower respiratory tract infection	**36**	**37**	**36**	**46**
Injection site reaction	**24**	**30**	**14**	**12**
Visual acuity reduced	**25**	**18**	**16**	**16**
Urinary tract infection	**15**	**20**	**18**	**16**
Eye pain	**11**	**30**	**13**	**8**
Conjunctival haemorrhage	**19**	**17**	**12**	**10**
Headache	**15**	**16**	**14**	**12**
Dizziness	**12**	**17**	**11**	**13**
Nasopharyngitis	**13**	**22**	**11**	**5**
Number and type of serious adverse events				
SAE	**81**	**69**	**83**	**83**

SAR	**4**	**6**	**4**	**4**
SUSAR	**3**	**1**	**2**	**1**
TOTAL	**88**	**76**	**83**	**88**

All data are n (%) unless otherwise indicated.

[†]Thought to be related to treatment

[‡] All data are n unless otherwise indicated.