

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Inclusion and exclusion criteria from the RIVAL study

<p>Inclusion criteria</p>	<p><i>Inclusion criteria for participant:</i></p> <ol style="list-style-type: none"> 1. Written informed consent must be obtained before any study-related assessment is performed. 2. Male or female participants ≥ 50 years of age. <p><i>Inclusion criteria for study eye:</i></p> <ol style="list-style-type: none"> 3. Diagnosis of active subfoveal CNV secondary to nAMD without restriction of lesion size, with visual impairment being exclusively due to an active nAMD lesion. Active lesions will be characterised by any of the following: abnormal retinal thickness, with evidence of intraretinal, subretinal or sub-pigment epithelial fluid accumulation, confirmed by OCT; presence of intraretinal or subretinal haemorrhage; leakage shown on a FA unless solely due to dry, fibrotic staining; visual acuity deterioration considered likely to represent CNV. 4. BCVA letter score at both Screening and Baseline must be 23 letters or more as measured by the 3 metre ETDRS-like charts, inclusively (or approximate Snellen equivalent to 3/60+3). <p>If both eyes are eligible at Screening and Baseline, the investigator will decide the study eye based on clinical judgment. Only one eye needs to meet the study entry criteria.</p>
<p>Exclusion criteria</p>	<p><i>Exclusion criteria for participant:</i></p> <ol style="list-style-type: none"> 1. Inability to comply with study or follow-up procedures. 2. Pregnant or nursing (lactating) women. 3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. <p><i>Exclusion criteria for systemic medical history and conditions:</i></p> <ol style="list-style-type: none"> 4. Any type of systemic disease or its treatment, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the participant to a significant degree or put the participant at special risk. 5. Stroke or myocardial infarction less than 3 months prior to Screening. 6. Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg at Screening or Baseline. 7. Known hypersensitivity to ranibizumab or aflibercept or any component of the ranibizumab or aflibercept formulation, or fluorescein. <p><i>Exclusion criteria for ocular medical history and conditions:</i></p> <p><i>For both eyes:</i></p> <ol style="list-style-type: none"> 8. Any active periocular or ocular infection or inflammation (e.g. blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline. 9. One or more patches of geographic atrophy $> 250\mu\text{m}$ in longest linear dimension. 10. Uncontrolled glaucoma (intraocular pressure ≥ 30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline. 11. Neovascularisation of the iris or neovascular glaucoma at the time of Screening or Baseline. 12. Inability of obtaining multimodal images of sufficient quality to be analysed. <p><i>For study eye:</i></p> <ol style="list-style-type: none"> 13. Visually significant cataract (likely to require surgery within the next 12 months), aphakia, severe vitreous haemorrhage, rhegmatogenous retinal detachment, proliferative diabetic retinopathy or CNV of any cause other than nAMD (e.g., ocular histoplasmosis, pathologic myopia macular hole) at the time of Screening and Baseline. 14. Structural damage within 0.5 disc diameter of the centre of the macula (e.g. vitreomacular traction, epiretinal membrane, scar, laser burn, foveal atrophy) at the time of

	<p>screening that in the investigator's opinion could preclude visual function improvement with treatment.</p> <p><i>Exclusion criteria for prior or current systemic medication:</i></p> <p>15. Use of other investigational drugs within 30 days or 5 half-lives from baseline, whichever is longer.</p> <p>16. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve as outlined in the study treatments Product Information.</p> <p><i>Exclusion criteria for prior or current ocular treatment:</i></p> <p><i>For study eye:</i></p> <p>17. Treatment with any anti-angiogenic drugs (including any anti-VEGF agents) prior to Baseline in eye.</p> <p>18. Any intraocular procedure (including Yttrium-Aluminium-Garnet capsulotomy) within 2 months prior to Baseline or anticipated within the next 6 months following Baseline.</p> <p><i>Exclusion criteria of prohibited treatments (study eye):</i></p> <p>19. Intra or periocular corticosteroids (including sub tenon but excluding topical formulations)</p> <p>20. Intraocular corticosteroid implants</p> <p>Treatment with any anti-angiogenic drug (including any anti-VEGF agents) is allowed prior to Baseline in fellow eye.</p>
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BCVA = best corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = Fluorescein Angiography; nAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography; VEGF = vascular endothelial growth factor.

eTable 2. Best-corrected visual acuity (BCVA) letter score and Change in BCVA from Baseline to the last visit of participants who withdrew from the study prior to Month 12 collapsed

Parameter/ Visit	Ranibizumab (N=14)	Aflibercept (N=16)
Baseline BCVA letter score [approx. Snellen equivalent]		
n	14	16
Mean±SD	59.0±17.27 [20/62.5]	62.8±12.11 [20/50]
Median (min, max)	61.0 (23, 86) [20/62.5]	62.5 (33, 82) [20/50]
BCVA letter score at last visit prior to Month 12 [approx. Snellen equivalent]		
n	14	16
Mean±SD	66.1±19.39 [20/50]	64.8±16.89 [20/50]
Median (min, max)	72.5 (13, 89) [20/32]	70.0 (20, 85) [20/40]
Change in BCVA letter score from Baseline*		
n	14	16
Mean±SD	7.1±9.90	2.0±14.67
Median (min, max)	5.5 (-10, 23)	3.0 (-25, 37)

* The last available non-missing value collected just prior to the start of treatment in the study eye.
BCVA = best-corrected visual acuity; SD = standard deviation

eTable 3. Injections in participants who withdrew from the study prior to Month 12.

	Ranibizumab (N=141)	Aflibercept (N=137)
n	14	16
Mean number of injections	5.1	6.2
SD	3.91	2.37
Median	3.5	6.0
Minimum	1	3
Maximum	13	11

SD: Standard Deviation

Follow-up period: from baseline (first dosing) to withdrawal dates (prior to Month 12).

eTable 4. Distribution injection intervals at Month 12.

Visit	Interval	Ranibizumab (N=141)	Aflibercept (N=137)
Month 12	n	130	123
	4 Weeks	62 (47.7%)	59 (48.0%)
	6 Weeks	18 (13.8%)	16 (13.0%)
	8 Weeks	11 (8.5%)	16 (13.0%)
	10 Weeks	12 (9.2%)	12 (9.8%)
	12 Weeks	27 (20.8%)	20 (16.3%)

Interval: planned retreatment decision interval at the last visit prior to Month 12 i.e. the last visit for each subject with a study day between 281 and 365

eTable 5. Number of visits in the first 12 months.

<u>Number of Visits</u>	Ranibizumab (N=141)	Aflibercept (N=137)
n	141	137
Mean	14.0	14.0
SD	3.20	2.77
25th Percentile	12.0	12.0
Median	14.0	14.0
75th Percentile	17.0	17.0
Minimum	3	6
Maximum	18	18

SD: Standard Deviation

Including all visits to the Month 12 visit, if Month 12 visit is present, or including all visits with study day \leq 365 days, if Month 12 visit is missing.

Screening and Baseline are each counted as a visit, even if carried out on the same day.

If the Month 12 visit was carried out on the same day as another visit, eg: Week 52, each are counted as a visit.

eTable 6. Distribution of numbers of visits in the first 12 months.

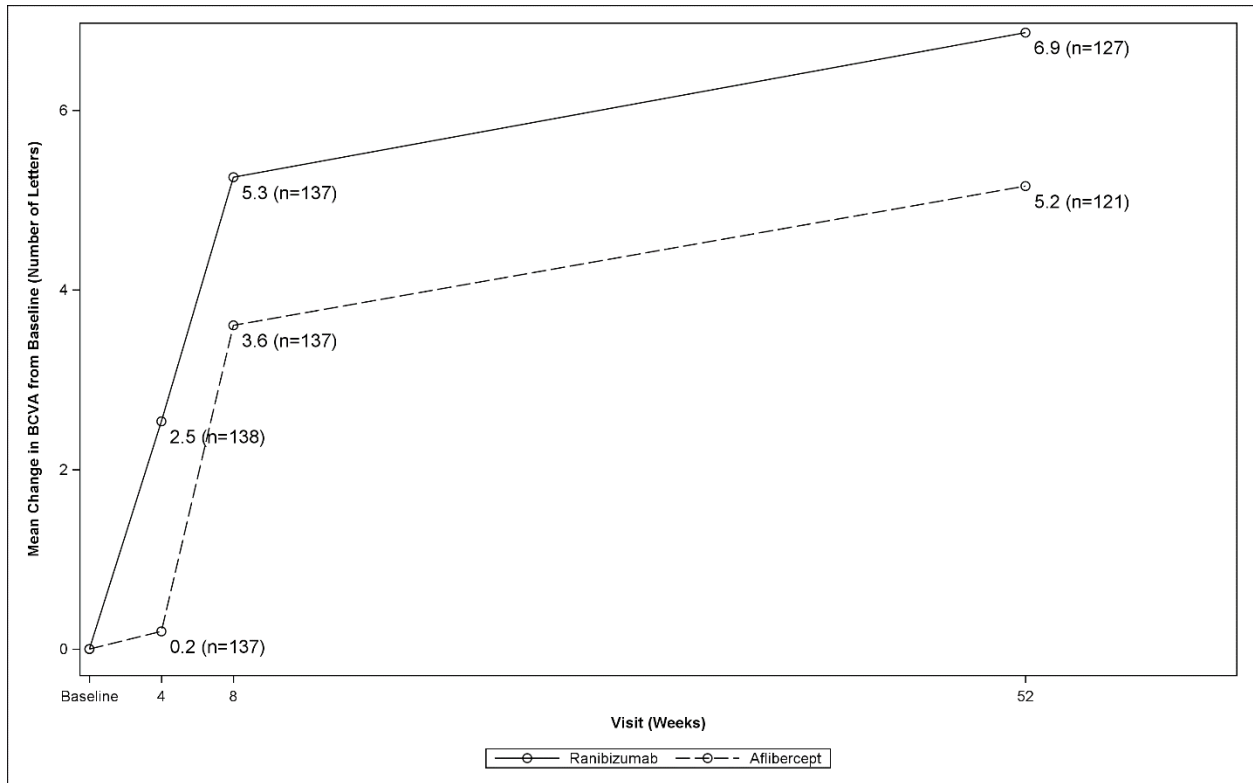
Number of Visits	Ranibizumab (N=141)	Aflibercept (N=137)
1	0	0
2	0	0
3	3 (2.1%)	0
4	1 (0.7%)	0
5	0	0
6	1 (0.7%)	2 (1.5%)
7	2 (1.4%)	1 (0.7%)
8	1 (0.7%)	1 (0.7%)
9	1 (0.7%)	2 (1.5%)
10	1 (0.7%)	4 (2.9%)
11	17 (12.1%)	16 (11.7%)
12	14 (9.9%)	18 (13.1%)
13	19 (13.5%)	18 (13.1%)
14	12 (8.5%)	11 (8.0%)
15	14 (9.9%)	16 (11.7%)
16	18 (12.8%)	13 (9.5%)
17	25 (17.7%)	21 (15.3%)
18	12 (8.5%)	14 (10.2%)

Including all visits to the Month 12 visit, if Month 12 visit is present, or including all visits with study day <=365 days, if Month 12 visit is missing.

Screening and Baseline are each counted as a visit, even if carried out on the same day.

If the Month 12 visit was carried out on the same day as another visit, eg: Week 52, each are counted as a visit

eFigure. Mean Change in Best-Corrected Visual Acuity from Baseline to Month 12, by Treatment Arm.



BCVA = best-corrected visual acuity.

eAppendix. List of RIVAL study investigators:

Dr Alan Luckie (Eye Clinic Albury Wodonga, Albury, NSW); A/Prof. Alex Hunyor (Retina Services Chatswood, Chatswood, NSW); Dr Andrew Chang (Sydney Retina & Day Clinic, Sydney); A/Prof Andrew Symons (Royal Melbourne Hospital, Parkville, VIC); A/Prof. Anthony Kwan (Queensland Eye Institute, Brisbane, QLD); Dr Brendan Vote (Launceston Eye Institute, South Launceston, TAS); Dr. Chris Kennedy (St John of God Eye Clinic, Subiaco, WA); Dr Christine Chen (Monash Medical Centre, Clayton, VIC); Dr Claire Hooper (Northern Beaches Retina, Brookvale, NSW); Dr Derek Chan (Marsden Eye Specialists, Parramatta, NSW); Dr Derek Chan (Retina Consultants, Hurstville, NSW); Dr Grant Raymond (Royal Adelaide Hospital, Adelaide, SA); Dr Graham Hay-Smith (Caboolture Eye Surgery, Brisbane, QLD); Dr Gurmit Uppal (Peninsula Eye Hospital, Brisbane, QLD); Prof. Ian McAllister (Lions Eye Institute, Nedlands, WA); Dr. Jagjit Singh 'Jolly' Gilhotra (Adelaide Eye and Retina Centre, Adelaide, SA); Dr James Wong (Strathfield Retina Clinic, Strathfield, NSW); Dr John Chang (Retina and Vitreous Centre, Strathfield, NSW); Prof. Mark Gillies (Save Sight Institute, Sydney, NSW); Dr Mark Gorbatov (Retina and Vitreous Centre, Sydney, NSW); Dr Paul Beaumont (Eye Doctors Mona Vale, Mona Vale, NSW); Prof. Paul Mitchell (Sydney West Retina, Westmead, NSW); Dr Paul Ng (Outlook Eye Specialists, Southport, QLD); A/Prof Wilson Heriot (Eye Surgery Associates, Malvern, VIC).