Clinical trial results:
Five year observational follow-up of the IVAN trial cohort: a study of function and morphology

Summary

EudraCT number	2015-002608-97
Trial protocol	GB
Global end of trial date	01 December 2017

Results information

Result version number	v1 (current)
This version publication date	24 March 2019
First version publication date	24 March 2019

Trial information

Trial identification

Sponsor protocol code	14206UC-AC

Additional study identifiers

ISRCTN number	ISRCTN92166560
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health & Social Care Trust
Sponsor organisation address	Research Office, 2nd Floor King Edward Building, Royal Hospitals, Grosvenor Road, Belfast, United Kingdom, BT12 6BA
Public contact	Usha Chakravarthy, Belfast Health and Social Care Trust, +44 02890632527, u.chakravarthy@qub.ac.uk
Scientific contact	Usha Chakravarthy, Belfast Health and Social Care Trust, +44 02890632527, alison.murphy@belfasttrust.hscni.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2017
Global end of trial reached?	Yes
Global end of trial date	01 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the care of IVAN participants in the NHS, and changes to their vision, since the end of the IVAN trial in order to better inform future NHS strategies for treatment of wet Age-related Macular Degeneration.
To compare outcomes by original randomised allocations at 5-7 years after randomisation.

Protection of trial subjects:

Participants were in an observational study of usual care during a period after IMP was discontinued and the trial was closed. This was a follow up study of long term outcomes and participants were not put at any risk.

Background therapy:

Not applicable- see above

Evidence for comparator:

Not applicable- see above

Actual start date of recruitment	26 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 532
Worldwide total number of subjects	532
EEA total number of subjects	532

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19

From 65 to 84 years	384
85 years and over	129

Subject disposition

Recruitment

Recruitment details:

All participants who did not die or withdraw from the IVAN trial were invited to participate in the follow up study by either attending a single research visit in person, for eye examinations and a questionnaire, or completing a questionnaire by post. They were also be offered the option to withdraw from the study.

Pre-assignment

Screening details:

Of the 610 patients recruited to the IVAN trial, 532 were included in the follow-up study; 66 died or withdrew during the IVAN trial, 7 were at a single site that did not participate in the extended IVAN follow up and 5 withdrew during the extended follow up. 124 of the 532 participants had died by the time of follow up.

Period 1

Period 1 title	Follow-up cohort (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The participants were initially randomised to one of four treatment regimens in the original IVAN trial, and participants, clinical and trial personnel were masked. At the start of this study, after exiting the trial, participants were treated in the NHS. Although health professionals and participants have not been masked to ongoing care, ophthalmologists managing participants are extremely unlikely to know the original experimental allocation

Arms

Are arms mutually exclusive?	No
Arm title	Follow-up cohort

Arm description:

All participants in the extended follow-up study

Of the 532 participants in the extended follow-up study, 124 had died and 199 agreed to attend a specific research visit. Data were collected passively for non-attenders (124 deceased patients and 209 who did not wish to attend a research visit)

Arm type	Overall

No investigational medicinal product assigned in this arm

Arm title	IVAN randomised allocation: Ranibizumab

Arm description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Arm type	IVAN trial allocation (reference group)
Investigational medicinal product name	Lucentis
Investigational medicinal product code	
Other name	Ranibizumab
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Drug dose during IVAN trial: 0.5 mg

Arm title	IVAN randomised allocation: Bevacizumab

Arm description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Arm type	IVAN trial allocation
Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Drug dose during IVAN trial: 1.25 mg

Arm title	IVAN randomised allocation: Continuous

Arm description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Arm type	IVAN trial allocation (reference group)

No investigational medicinal product assigned in this arm

Arm title	IVAN randomised allocation: Discontinuous

Arm description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Arm type	IVAN trial allocation

No investigational medicinal product assigned in this arm

Arm title	Intralesional macular atrophy (ILMA) absent in study eye

Arm description:

Intralesional macular atrophy (ILMA) absent in study eye at extended follow up.

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Arm type	ILMA (reference)

No investigational medicinal product assigned in this arm

Arm title	Intralesional macular atrophy (ILMA) present in study eye

Arm description:

Intralesional macular atrophy (ILMA) present in study eye at extended follow up

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Arm type	ILMA

No investigational medicinal product assigned in this arm

Arm title	Geographic atrophy (GA) absent in study eye

Arm description:

Geographic atrophy (GA) absent in study eye at extended follow up

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Arm type	GA (reference)
No investigational medicinal product assigned in this arm	
Arm title	Geographic atrophy (GA) present in study eye

Arm description:

Geographic atrophy (GA) present in study eye at extended follow up

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Arm type	GA
No investigational medicinal product assigned in this arm	
Arm title	Developed/worsened intralesional macular atrophy (ILMA)

Arm description:

Defined as the development (incident) or expansion of the area (worsened) of ILMA. Expansion of the area of ILMA was quantified and was classified as worsened when it increased by >20%

Arm type	ILMA
No investigational medicinal product assigned in this arm	
Arm title	Did not develop/worsen intralesional macular atrophy (ILMA)

Arm description:

Defined as the development (incident) or expansion of the area (worsened) of ILMA. Expansion of the area of ILMA was quantified and was classified as worsened when it increased by >20%

Arm type	ILMA
No investigational medicinal product assigned in this arm	
Arm title	Developed/worsend geographic atrophy (GA)

Arm description:

Defined as the development (incident) or expansion of the area (worsened) of GA. Expansion of the area of GA was quantified and was classified as worsened when it increased by >20%.

Arm type	GA
No investigational medicinal product assigned in this arm	
Arm title	Did not develop/worsen geographic atrophy (GA)

Arm description:

Defined as the development (incident) or expansion of the area (worsened) of GA. Expansion of the area of GA was quantified and was classified as worsened when it increased by >20%.

Arm type	GA
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab
Started	532	272	260
Completed	532	272	260

Number of subjects in period 1	IVAN randomised allocation: Continuous	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye
Started	269	263	122

Completed	269	263	122

Number of subjects in period 1	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye	Geographic atrophy (GA) present in study eye
Started	346	309	159
Completed	346	309	159

Number of subjects in period 1	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Started	243	138	142
Completed	243	138	142

Number of subjects in period 1	Did not develop/worsen geographic atrophy (GA)
Started	311
Completed	311

Baseline characteristics

Reporting groups	
Reporting group title	Follow-up cohort

Reporting group description: -

Reporting group values	Follow-up cohort	Total	
Number of subjects	532	532	
Age categorical			
Age at IVAN exit			
Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	384	384	
85 years and over	129	129	
Age continuous			
Age at IVAN exit			
Units: years			
arithmetic mean	79.4		
standard deviation	± 7.4	-	
Gender categorical			
Units: Subjects			
Female	320	320	
Male	212	212	
Drug			
Drug allocation during IVAN trial			
Units: Subjects			
Ranibizumab	272	272	
Bevacizumab	260	260	
Drug frequency			
Treatment regimen during IVAN trial			
Units: Subjects			
Continuous	269	269	
Discontinuous	263	263	
Angina at IVAN entry			
Units: Subjects			
Yes	72	72	
No	460	460	
Dyspnoea at IVAN entry			
Units: Subjects			
Yes	97	97	
No	433	433	
Missing	2	2	
Dyspnoea at IVAN exit			
Units: Subjects			
Yes	106	106	
No	424	424	
Missing	2	2	
Myocardial infarction at IVAN entry			

Units: Subjects			
Yes	37	37	
No	495	495	
Transient ischemic attack at IVAN entry Units: Subjects			
Yes	26	26	
No	477	477	
Missing	29	29	
Stroke at IVAN entry Units: Subjects			
Yes	8	8	
No	524	524	
DVT/PE at IVAN entry			
DVT = deep vein thrombosis; PE =pulmonary embolism			
Units: Subjects			
Yes	30	30	
No	501	501	
Missing	1	1	
Current or past smoker at IVAN entry Units: Subjects			
Yes	331	331	
No	197	197	
Missing	4	4	
Systolic BP at IVAN entry			
BP = Blood pressure			
Units: mmHg			
arithmetic mean	142.4		
standard deviation	± 19.2	-	
Diastolic BP at IVAN entry			
BP = Blood pressure			
Units: mmHg			
arithmetic mean	77.0		
standard deviation	± 10.2	-	
Systolic BP at IVAN exit			
BP = Blood pressure Data missing for 8 patients (3 Attenders, 1 Survivor, passive data collection only, 4 Deceased, passive data collection only)			
Units: mmHG			
arithmetic mean	138.5		
standard deviation	± 18.9	-	
Diastolic BP at IVAN exit			
BP = Blood pressure Data missing for 8 patients (3 Attenders, 1 Survivor, passive data collection only, 4 Deceased, passive data collection only)			
Units: mmHg			
arithmetic mean	74.3		
standard deviation	± 10.2	-	

Subject analysis sets

Subject analysis set title	Attenders
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who attended a research visit as part of the IVAN follow-up study.

196/199 (98.5%) have at least one ophthalmology appointment as part of usual care since IVAN exit
Length of follow up during usual care since IVAN entry (years, Median IQR): 6.8 (6.1, 7.4)
Length of follow up during usual care since IVAN exit (years, Median IQR): 4.8 (4.2, 5.4)

Length of follow up to research appointment since IVAN entry (years, Median IQR): 7.3 (6.8, 7.8)
Length of follow up to research appointment since IVAN exit (years, Median IQR): 5.3 (4.8, 5.8)

Subject analysis set title	Survivor, passive data collection only
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Non-attenders (passive data collection only) - survivors

198/209 (94.7%) have at least one ophthalmology appointment as part of usual care since IVAN exit
Length of follow up during usual care since IVAN entry (years, Median IQR): 6.3 (4.3, 7.4)
Length of follow up during usual care since IVAN exit (years, Median IQR): 4.4 (2.3, 5.4)

Subject analysis set title	Deceased, passive data collection only
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Non-attenders (passive data collection only) - deceased

112/124 (90.3%) have at least one ophthalmology appointment as part of usual care since IVAN exit
Length of follow up during usual care since IVAN entry (years, Median IQR): 3.8 (3.0, 4.8)
Length of follow up during usual care since IVAN exit (years, Median IQR): 1.7 (1.1, 2.8)

Reporting group values	Attenders	Survivor, passive data collection only	Deceased, passive data collection only
Number of subjects	199	209	124
Age categorical			
Age at IVAN exit			
Units: Subjects			
Adults (18-64 years)	9	10	0
From 65-84 years	166	144	74
85 years and over	24	55	50
Age continuous			
Age at IVAN exit			
Units: years			
arithmetic mean	76.5	79.6	83.8
standard deviation	± 7.0	± 7.5	± 5.4
Gender categorical			
Units: Subjects			
Female	114	138	68
Male	85	71	56
Drug			
Drug allocation during IVAN trial			
Units: Subjects			
Ranibizumab	105	105	62
Bevacizumab	94	104	62
Drug frequency			
Treatment regimen during IVAN trial			
Units: Subjects			
Continuous	101	103	65
Discontinuous	98	106	59
Angina at IVAN entry			
Units: Subjects			

Yes	19	25	28
No	180	184	96
Dyspnoea at IVAN entry Units: Subjects			
Yes	25	39	33
No	173	169	91
Missing	1	1	0
Dyspnoea at IVAN exit Units: Subjects			
Yes	31	41	34
No	168	168	88
Missing	0	0	2
Myocardial infarction at IVAN entry Units: Subjects			
Yes	7	14	16
No	192	195	108
Transient ischemic attack at IVAN entry Units: Subjects			
Yes	7	11	8
No	180	188	109
Missing	12	10	7
Stroke at IVAN entry Units: Subjects			
Yes	3	2	3
No	196	207	121
DVT/PE at IVAN entry			
DVT = deep vein thrombosis; PE =pulmonary embolism			
Units: Subjects			
Yes	8	9	13
No	191	199	111
Missing	0	1	0
Current or past smoker at IVAN entry Units: Subjects			
Yes	113	128	90
No	83	81	33
Missing	3	0	1
Systolic BP at IVAN entry			
BP = Blood pressure			
Units: mmHg			
arithmetic mean	140.6	143.1	144.0
standard deviation	± 17.7	± 19.6	± 20.7
Diastolic BP at IVAN entry			
BP = Blood pressure			
Units: mmHg			
arithmetic mean	76.7	78.3	75.0
standard deviation	± 9.0	± 10.3	± 11.6
Systolic BP at IVAN exit			
BP = Blood pressure Data missing for 8 patients (3 Attenders, 1 Survivor, passive data collection only, 4 Deceased, passive data collection only)			
Units: mmHG			
arithmetic mean	137.3	140.2	137.6

standard deviation	± 17.2	± 18.9	± 21.5
Diastolic BP at IVAN exit			
BP = Blood pressure Data missing for 8 patients (3 Attenders, 1 Survivor, passive data collection only, 4 Deceased, passive data collection only)			
Units: mmHg			
arithmetic mean	75.4	74.9	71.6
standard deviation	± 9.3	± 10.4	± 10.9

End points

End points reporting groups

Reporting group title	Follow-up cohort

Reporting group description:

All participants in the extended follow-up study

Of the 532 participants in the extended follow-up study, 124 had died and 199 agreed to attend a specific research visit. Data were collected passively for non-attenders (124 deceased patients and 209 who did not wish to attend a research visit)

Reporting group title	IVAN randomised allocation: Ranibizumab

Reporting group description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Reporting group title	IVAN randomised allocation: Bevacizumab

Reporting group description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Reporting group title	IVAN randomised allocation: Continuous

Reporting group description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Reporting group title	IVAN randomised allocation: Discontinuous

Reporting group description:

This is an observational follow up of the original participants who were enrolled in the IVAN trial. The participants were initially randomised to one of four treatment regimens in the original IVAN trial and after exiting the trial, participants were treated in the NHS. The follow up study looked at the long term outcomes of these patients and is purely observational in that there was data collection but no intervention. This arm is the treatment allocation of the original IVAN trial.

Reporting group title	Intralesional macular atrophy (ILMA) absent in study eye

Reporting group description:

Intralesional macular atrophy (ILMA) absent in study eye at extended follow up.

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Reporting group title	Intralesional macular atrophy (ILMA) present in study eye

Reporting group description:

Intralesional macular atrophy (ILMA) present in study eye at extended follow up

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Reporting group title	Geographic atrophy (GA) absent in study eye

Reporting group description:

Geographic atrophy (GA) absent in study eye at extended follow up

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Reporting group title	Geographic atrophy (GA) present in study eye

Reporting group description:

Geographic atrophy (GA) present in study eye at extended follow up

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA)) during extended follow up.

Reporting group title	Developed/worsened intralesional macular atrophy (ILMA)

Reporting group description:

Defined as the development (incident) or expansion of the area (worsened) of ILMA. Expansion of the area of ILMA was quantified and was classified as worsened when it increased by >20%

Reporting group title	Did not develop/worsen intralesional macular atrophy (ILMA)

Reporting group description:

Defined as the development (incident) or expansion of the area (worsened) of ILMA. Expansion of the area of ILMA was quantified and was classified as worsened when it increased by >20%

Reporting group title	Developed/worsend geographic atrophy (GA)

Reporting group description:

Defined as the development (incident) or expansion of the area (worsened) of GA. Expansion of the area of GA was quantified and was classified as worsened when it increased by >20%.

Reporting group title	Did not develop/worsen geographic atrophy (GA)

Reporting group description:

Defined as the development (incident) or expansion of the area (worsened) of GA. Expansion of the area of GA was quantified and was classified as worsened when it increased by >20%.

Subject analysis set title	Attenders
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who attended a research visit as part of the IVAN follow-up study.

196/199 (98.5%) have at least one ophthalmology appointment as part of usual care since IVAN exit
Length of follow up during usual care since IVAN entry (years, Median IQR): 6.8 (6.1, 7.4)
Length of follow up during usual care since IVAN exit (years, Median IQR): 4.8 (4.2, 5.4)

Length of follow up to research appointment since IVAN entry (years, Median IQR): 7.3 (6.8, 7.8)
Length of follow up to research appointment since IVAN exit (years, Median IQR): 5.3 (4.8, 5.8)

Subject analysis set title	Survivor, passive data collection only
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Non-attenders (passive data collection only) - survivors

198/209 (94.7%) have at least one ophthalmology appointment as part of usual care since IVAN exit
Length of follow up during usual care since IVAN entry (years, Median IQR): 6.3 (4.3, 7.4)
Length of follow up during usual care since IVAN exit (years, Median IQR): 4.4 (2.3, 5.4)

Subject analysis set title	Deceased, passive data collection only
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Non-attenders (passive data collection only) - deceased

112/124 (90.3%) have at least one ophthalmology appointment as part of usual care since IVAN exit
Length of follow up during usual care since IVAN entry (years, Median IQR): 3.8 (3.0, 4.8)
Length of follow up during usual care since IVAN exit (years, Median IQR): 1.7 (1.1, 2.8)

Primary: Development of intralesional macular atrophy (ILMA)

End point title	Development of intralesional macular atrophy (ILMA)

End point description:

ILMA = intralesional macular atrophy (defined as atrophy lying within the footprint of the neovascular lesion); Primary morphology outcome

Study eyes with ILMA at IVAN exit (baseline) were excluded from this analysis. Missing data imputed using multiple imputation methods.

We had intended to examine the impact of HRM type (well or ill defined). However, review of the OCT data did not support dichotomising participant eyes based on HRM. HRM was therefore modelled as present vs. absent.

ILMA= Intralesional macular atrophy, GA= Geographic atrophy, FU=Follow up, CNV= Choroidal neovascularisation, HRM= Hyperreflective material, PED= Pigment Epithelial Detachment, SRF= Subretinal fluid, nAMD= neovascular age-related macular degeneration, CI=Confidence interval

End point type	Primary

End point timeframe:

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA))

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	319[1]	167[2]	152[3]	157[4]
Units: Patients				
Developed ILMA	197	101	96	59
Did not develop ILMA	122	66	56	59

Notes:

[1] - Exclusions: a) No images available (n=64). b) ILMA at baseline (n=149).

[2] - Exclusions: a) No images available (n=27). b) ILMA at baseline (n=78).

[3] - Exclusions: a) No images available (n=37). b) ILMA at baseline (n=71).

[4] - Exclusions: a) No images available (n=35). b) ILMA at baseline (n=77).

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	162[5]	122	197[6]	225[7]
Units: Patients				
Developed ILMA	63	0	197	109
Did not develop ILMA	63	122	0	116

Notes:

[5] - Exclusions: a) No images available (n=29). b) ILMA at baseline (n=72).

[6] - Exclusions: ILMA at baseline (n=149)

[7] - Exclusions: a) ILMA at baseline (n=84).

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94[8]	197[9]	122[10]	84[11]
Units: Patients				
Developed ILMA	88	197	0	78

Did not develop ILMA	6	0	122	6

Notes:

[8] - Exclusions: a) ILMA at baseline (n=65).

[9] - Exclusions: a) ILMA at baseline (n=46).

[10] - Exclusions: a) ILMA at baseline (n=16).

[11] - Exclusions: a) ILMA at baseline (n=58).

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	225[12]			
Units: Patients				
Developed ILMA	109			
Did not develop ILMA	116			

Notes:

[12] - Exclusions: a) ILMA at baseline (n=86).

Statistical analyses

Statistical analysis title	Effect of age at IVAN exit (per 10 years)

Statistical analysis description:

Multivariable model adjusted for:
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	2.62

Statistical analysis title	Effect of gender (male)

Statistical analysis description:

Multivariable model adjusted for:

Age at IVAN exit (per 10 years)
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.28

Statistical analysis title	Effect of IVAN trial drug allocation (Bevacizumab)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) present in study eye v Intralesional macular atrophy (ILMA) absent in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.519
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.98

Statistical analysis title	Effect of IVAN trial treatment regimen (Discont.)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug allocation during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.879
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.61

Statistical analysis title	Effect of injection rate during EFU (per year)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) present in study eye v Intralesional macular atrophy (ILMA) absent in study eye

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.021
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	0.98

Statistical analysis title	Effect of >50% classic CNV at IVAN entry

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.173
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.2

Statistical analysis title	Effect of retinal thickness at IVAN exit(per 10µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10mm)

SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.068
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.07

Statistical analysis title	Effect of subretinal fluid (SRF) at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.676
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.6

Statistical analysis title	Effect of PED at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.359
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.6

Statistical analysis title	Effect of PED at EFU (at fovea height <85µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	= 0.115 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.75

Notes:

[13] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent
[14] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent at fovea)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 0.115 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	5.14

Notes:

[15] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent
[16] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) present in study eye v Intralesional macular atrophy (ILMA) absent in study eye

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence[17]
P-value	= 0.115 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	5.37

Notes:

[17] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent
[18] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of HRM at EFU

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) present in study eye v Intralesional macular atrophy (ILMA) absent in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.833
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.99

Statistical analysis title	Effect of ILMA FE at IVAN exit (ILMA present)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender

Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	= 0.937 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3.88

Notes:

[19] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[20] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of ILMA FE at IVAN exit (no nAMD lesion)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE
GA in FE at IVAN exit

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence[21]
P-value	= 0.937 [22]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.8

Notes:

[21] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[22] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of GA in FE at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)

Comparison groups	Intralesional macular atrophy (ILMA) present in study eye v Intralesional macular atrophy (ILMA) absent in study eye
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.106
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	9.91

Primary: Final distance visual acuity (DVA) in study eye

End point title	Final distance visual acuity (DVA) in study eye

End point description:

DVA was the primary visual function outcome

End point type	Primary

End point timeframe:

DVA in study eye (most recent reading during extended FU, including research appointment for attenders).

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	508[23]	262[24]	246[25]	257[26]
Units: Letters				
median (inter-quartile range (Q1-Q3))	57 (29.5 to 71.5)	57.5 (30.0 to 72.0)	57.0 (28.0 to 71.0)	53.0 (30.0 to 73.0)

Notes:

[23] - Exclusions: No VA reading since IVAN exit (n=24)

[24] - Exclusions: No VA reading since IVAN exit (n=10)

[25] - Exclusions: No VA reading since IVAN exit (n=14)

[26] - Exclusions: No VA reading since IVAN exit (n=12)

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	251[27]	113[28]	315[29]	289[30]
Units: Letters				
median (inter-quartile range (Q1-Q3))	58.0 (29.0 to 70.0)	66.3 (47.0 to 74.2)	50.1 (27.6 to 67.6)	60.9 (39.4 to 71.5)

Notes:

[27] - Exclusions: No VA reading since IVAN exit (n=12)

[28] - Exclusions: Less than 5 VA readings since IVAN exit (n=9)

[29] - Exclusions: Less than 5 VA readings since IVAN exit (n=31)

[30] - Exclusions: Less than 5 VA readings since IVAN exit (n=20)

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	139[31]	243	138	141[32]
Units: Letters				
median (inter-quartile range (Q1-Q3))	38.5 (24.3 to 64.4)	52.0 (24.0 to 69.0)	64.5 (36.0 to 76.0)	41.0 (22.0 to 63.0)

Notes:

[31] - Exclusions: Less than 5 VA readings since IVAN exit (n=20)

[32] - Exclusions: No VA reading since IVAN exit (n=1)

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	310[33]			
Units: Letters				
median (inter-quartile range (Q1-Q3))	63.0 (34.0 to 73.0)			

Notes:

[33] - Exclusions: No VA reading since IVAN exit (n=1)

Statistical analyses

Statistical analysis title	Effect of trial drug allocation on DVA

Statistical analysis description:

The effects of the randomized allocations on DVA in the study eye at the most recent recorded visit was assessed using linear regression. These analyses were adjusted for centre size (seven strata as per the IVAN trial).

Excluding patients who do not have a DVA reading since IVAN exit (n=24)

Comparison groups	IVAN randomised allocation: Bevacizumab v IVAN randomised allocation: Ranibizumab
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6429
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	3.4

Statistical analysis title	Effect of trial treatment regimen on DVA

Statistical analysis description:

The effects of the randomized allocations on DVA in the study eye at the most recent recorded visit was assessed using linear regression. These analyses were adjusted for centre size (seven strata as per the IVAN trial).

Excluding patients who do not have a DVA reading since IVAN exit (24)

Comparison groups	IVAN randomised allocation: Continuous v IVAN randomised allocation: Discontinuous
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9917
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4.4

Statistical analysis title	Effect of ILMA on DVA

Statistical analysis description:

A linear random effects methods model was fitted to DVA readings between IVAN exit visit and the date of the image used to grade ILMA. From this model, participants' DVA values were predicted for the date

of the image used to grade ILMA. A linear regression model was then fitted to estimate associations between the presence of ILMA on predicated DVA. Analyses were adjusted for visual function at IVAN exit.

Excluding patients with no SE images (n=64) and patients with <5 DVA readings (n=40)

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0206
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	-0.8

Statistical analysis title	Effect of GA on DVA

Statistical analysis description:

A linear random effects methods model was fitted to DVA readings between IVAN exit visit and the date of the image used to grade ILMA. From this model, participants' DVA values were predicted for the date of the image used to grade ILMA. A linear regression model was then fitted to estimate associations between the presence of ILMA on predicated DVA. Analyses were adjusted for visual function at IVAN exit.

Excluding patients with no SE images (n=64) and patients with <5 DVA readings (n=40)

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0179
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	-0.9

Primary: Survival

End point title	Survival

End point description:

Survival was the primary safety outcome

End point type	Primary

End point timeframe:

Time to death since IVAN entry. Times were censored at most recent clinical review.

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	532	272	260	269
Units: Years				
median (inter-quartile range (Q1-Q3))	6.2 (4.3 to 7.2)	6.2 (4.4 to 7.2)	6.2 (4.2 to 7.3)	6.0 (4.3 to 7.1)

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	263	122	346	309
Units: Years				
median (inter-quartile range (Q1-Q3))	6.4 (4.4 to 7.3)	6.6 (4.7 to 7.3)	6.3 (4.8 to 7.3)	6.5 (5.0 to 7.3)

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	159	243	138	142
Units: Years				
median (inter-quartile range (Q1-Q3))	6.1 (4.4 to 7.1)	6.3 (5.1 to 7.3)	6.6 (4.7 to 7.3)	6.0 (4.4 to 7.0)

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	311			
Units: Years				
median (inter-quartile range (Q1-Q3))	6.5 (5.0 to 7.3)			

Statistical analyses

Statistical analysis title	Effect of trial drug allocation on survival

Statistical analysis description:

The effects of the randomized allocations on survival since IVAN entry was assessed using Cox proportional-hazards regression. These analyses were adjusted for centre size (seven strata as per the IVAN trial).

Comparison groups	IVAN randomised allocation: Ranibizumab v IVAN randomised allocation: Bevacizumab
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3789
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.67

Statistical analysis title	Effect of trial treatment regimen on survival

Statistical analysis description:

The effects of the randomized allocations on survival since IVAN entry was assessed using Cox proportional-hazards regression. These analyses were adjusted for centre size (seven strata as per the IVAN trial).

Comparison groups	IVAN randomised allocation: Continuous v IVAN randomised allocation: Discontinuous
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5115
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.27

Secondary: Development of geographic atrophy (GA)

End point title	Development of geographic atrophy (GA)

End point description:

GA = Geographic atrophy (defined as atrophy lying outside the footprint of the neovascular lesion)

Study eyes with GA at IVAN exit (baseline) were excluded from this analysis. Missing data imputed using multiple imputation methods.

ILMA= Intralesional macular atrophy, GA= Geographic atrophy, FU=Follow up, CNV= Choroidal neovascularisation, HRM= Hyperreflective material, PED= Pigment Epithelial Detachment, SRF= Subretinal fluid, nAMD= neovascular age-related macular degeneration, CI=Confidence interval

End point type	Secondary

End point timeframe:

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA))

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	448[34]	233[35]	215[36]	223[37]
Units: Patients				
Developed GA	139	78	61	62
Did not develop GA	309	155	154	161

Notes:

[34] - Exclusions: a) No images available (n=64). b) GA at baseline (n=20).

[35] - Exclusions: a) No images available (n=27). b) GA at baseline (n=12).

[36] - Exclusions: a) No images available (n=37). b) GA at baseline (n=8).

[37] - Exclusions: a) No images available (n=35). b) GA at baseline (n=11).

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	225[38]	122	326[39]	309
Units: Patients				
Developed GA	77	6	133	0
Did not develop GA	148	116	193	309

Notes:

[38] - Exclusions: a) No images available (n=29). b) GA at baseline (n=9).

[39] - Exclusions: a) GA at baseline (n=20).

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	139[40]	229[41]	137[42]	139[43]
Units: Patients				
Developed GA	139	87	6	139
Did not develop GA	0	142	131	0

Notes:

[40] - Exclusions: GA at baseline (n=20)

[41] - Exclusions: a) GA at baseline (n=14).

[42] - Exclusions: a) GA at baseline (n=1).

[43] - Exclusions: a) GA at baseline (n=3).

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	309[44]			
Units: Patients				
Developed GA	0			
Did not develop GA	309			

Notes:

[44] - Exclusions: a) GA at baseline (n=2).

Statistical analyses

Statistical analysis title	Effect of age at IVAN exit (per 10 years)

Statistical analysis description:

Multivariable model adjusted for:
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.49
upper limit	2.96

Statistical analysis title	Effect of gender (male)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit

PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.613
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.41

Statistical analysis title	Effect of IVAN trial drug allocation (Bevacizumab)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.136
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.12

Statistical analysis title	Effect of IVAN trial treatment regimen (Discont.)

Statistical analysis description:

Multivariable model adjusted for:

Age at IVAN exit (per 10 years)
Gender
Drug alliocation during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.079
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.37

Statistical analysis title	Effect of injection rate during EFU (per year)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.045
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	0.998

Statistical analysis title	Effect of >50% classic CNV at IVAN entry

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.518
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.06

Statistical analysis title	Effect of retinal thickness at IVAN exit(per 10µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.318
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.61

Statistical analysis title	Effect of subretinal fluid (SRF) at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) present in study eye v Geographic atrophy (GA) absent in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.67
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.57

Statistical analysis title	Effect of PED present at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.812
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.01

Statistical analysis title	Effect of PED at EFU (at fovea height <85µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[45]
P-value	= 0.003 [46]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.11

Notes:

[45] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[46] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent at fovea)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial

Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[47]
P-value	= 0.003 [48]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.51
upper limit	5.21

Notes:

[47] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent
[48] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[49]
P-value	= 0.003 [50]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	6.46

Notes:

[49] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent
[50] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of ILMA FE at IVAN exit (ILMA present)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[51]
P-value	= 0.974 [52]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	2.22

Notes:

[51] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[52] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of ILMA FE at IVAN exit (no nAMD lesion)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
GA in FE at IVAN exit

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence[53]
P-value	= 0.974 [54]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.62

Notes:

[53] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[54] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of GA in FE at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	6.32

Secondary: Development/worsening of intralesional macular atrophy (ILMA)

End point title	Development/worsening of intralesional macular atrophy (ILMA)

End point description:

ILMA = intralesional macular atrophy (defined as atrophy lying within the footprint of the neovascular lesion)

This outcome was defined as the development (incident) or expansion of the area (worsened) of ILMA. Expansion of the area of ILMA was quantified and was classified as worsened when it increased by >20%. The outcome was defined to include worsening of ILMA so that the analyses did not exclude study eyes with ILMA at baseline.

Missing data imputed using multiple imputation methods. We had intended to examine the impact of HRM type (well or ill defined). However, review of the OCT data did not support dichotomising participant eyes based on HRM. HRM was therefore modelled as present vs. absent.

ILMA= Intralesional macular atrophy, GA= Geographic atrophy, FU=Follow up, CNV= Choroidal neovascularisation, HRM= Hyperreflective material, PED= Pigment Epithelial Detachment, SRF= Subretinal fluid, nAMD= neovascular age-related macular degeneration, CI=Confidence interval

End point type	Secondary

End point timeframe:

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA))

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	381[55]	204[56]	177[57]	187[58]
Units: Patients				
Developed/worsened	243	130	113	120
Did not develop/worsen	138	74	64	67

Notes:

[55] - Exclusions: No images available since IVAN exit (n=64). Worsening unknown (n=87)

[56] - Exclusions: No images available since IVAN exit (n=27). Worsening unknown (n=41)

[57] - Exclusions: No images available since IVAN exit (n=37). Worsening unknown (n=46)

[58] - Exclusions: No images available since IVAN exit (n=35). Worsening unknown (n=47)

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	194[59]	122	259[60]	273[61]
Units: Patients				
Developed/worsened	123	0	243	142
Did not develop/worsen	71	122	16	131

Notes:

[59] - Exclusions: No images available since IVAN exit (n=29). Worsening unknown (n=40)

[60] - Exclusions: Worsening unknown (n=87)

[61] - Exclusions: Worsening unknown (n=36)

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108[62]	243	138	96[63]
Units: Patients				

Developed/worsened	101	243	0	89
Did not develop/worsen	7	0	138	7

Notes:

[62] - Exclusions: Worsening unknown (n=51)

[63] - Exclusions: Worsening unknown (n=46)

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	275[64]			
Units: Patients				
Developed/worsened	144			
Did not develop/worsen	131			

Notes:

[64] - Exclusions: Worsening unknown (n=36)

Statistical analyses

Statistical analysis title	Effect of age at IVAN exit (per 10 years)

Statistical analysis description:

Multivariable model adjusted for:
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	2.36

Statistical analysis title	Effect of gender (male)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Drug and treatment regimen during IVAN trial

Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.432
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.31

Statistical analysis title	Effect of IVAN trial drug allocation (Bevacizumab)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.539
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.82

Statistical analysis title	Effect of IVAN trial treatment regimen (Discont.)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug allocation during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.872
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.67

Statistical analysis title	Effect of injection rate during EFU (per year)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)

Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.089
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.01

Statistical analysis title	Effect of >50% classic CNV at IVAN entry

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.13
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.12

Statistical analysis title	Effect of retinal thickness at IVAN exit(per 10µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
SRF present at IVAN exit
PED present at IVAN exit

PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.311
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.61

Statistical analysis title	Effect of subretinal fluid (SRF) at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.497
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.43

Statistical analysis title	Effect of PED at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:

Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.835
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.86

Statistical analysis title	Effect of PED at EFU (at fovea height <85µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence[65]
P-value	= 0.115 [66]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.81

Notes:

[65] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[66] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent at fovea)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence[67]
P-value	= 0.115 [68]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	3.54

Notes:

[67] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[68] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v

	Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence[69]
P-value	= 0.115 [70]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	4.19

Notes:

[69] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[70] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of HRM at EFU

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.625
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.16

Statistical analysis title	Effect of ILMA FE at IVAN exit (ILMA present)

Statistical analysis description:

Multivariable model adjusted for:

Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence[71]
P-value	= 0.937 [72]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.91

Notes:

[71] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[72] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of ILMA FE at IVAN exit (no nAMD lesion)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
GA in FE at IVAN exit

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence[73]
P-value	= 0.937 [74]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.58

Notes:

[73] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[74] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of GA in FE at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
HRM present at EFU
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)

Comparison groups	Developed/worsened intralesional macular atrophy (ILMA) v Did not develop/worsen intralesional macular atrophy (ILMA)
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.325
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	3.84

Secondary: Development/worsening of geographic atrophy (GA)

End point title	Development/worsening of geographic atrophy (GA)

End point description:

GA = Geographic atrophy (defined as atrophy lying outside the footprint of the neovascular lesion)

This outcome was defined as the development (incident) or expansion of the area (worsened) of GA. Expansion of the area of GA was quantified and was classified as worsened when it increased by >20%. The outcome was defined to include worsening of GA so that the analyses did not exclude study eyes with ILMA at baseline.

Missing data imputed using multiple imputation methods.

We had intended to examine the impact of HRM type (well or ill defined). However, review of the OCT data did not support dichotomising participant eyes based on HRM. HRM was therefore modelled as present vs. absent.

ILMA= Intralesional macular atrophy, GA= Geographic atrophy, FU=Follow up, CNV= Choroidal neovascularisation, HRM= Hyperreflective material, PED= Pigment Epithelial Detachment, SRF= Subretinal fluid, nAMD= neovascular age-related macular degeneration, CI=Confidence interval

End point type	Secondary

End point timeframe:

Determined using most recent image available (color fundus photography, blue light autofluorescence (AF), optical coherence tomography (OCT) or dye angiography fluorescein/indocyanine green (FFA))

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	453[75]	236[76]	217[77]	226[78]
Units: Patients				
Developed/worsened	142	79	63	64
Did not develop/worsen	311	157	154	162

Notes:

[75] - Exclusions: No images available since IVAN exit (n=64). Worsening unknown (n=15)

[76] - Exclusions: No images available since IVAN exit (n=27). Worsening unknown (n=9)

[77] - Exclusions: No images available since IVAN exit (n=37). Worsening unknown (n=6)

[78] - Exclusions: No images available since IVAN exit (n=35). Worsening unknown (n=8)

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	227[79]	122	331[80]	309
Units: Patients				
Developed/worsened	78	6	136	0
Did not develop/worsen	149	116	195	309

Notes:

[79] - Exclusions: No images available since IVAN exit (n=29). Worsening unknown (n=7)

[80] - Exclusions: Worsening unknown (n=15)

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	144[81]	233[82]	138	142
Units: Patients				
Developed/worsened	142	89	7	142
Did not develop/worsen	2	144	131	0

Notes:

[81] - Exclusions: Worsening unknown (n=15)

[82] - Exclusions: Worsening unknown (n=10)

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	311			
Units: Patients				
Developed/worsened	0			
Did not develop/worsen	311			

Statistical analyses

Statistical analysis title	Effect of age at IVAN exit (per 10 years)

Statistical analysis description:

Multivariable model adjusted for:
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	2.83

Statistical analysis title	Effect of gender (male)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.77
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.48

Statistical analysis title	Effect of IVAN trial drug allocation (Bevacizumab)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.233
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.19

Statistical analysis title	Effect of IVAN trial treatment regimen (Discont.)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender

Drug allocation during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.098
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	2.27

Statistical analysis title	Effect of injection rate during EFU (per year)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Did not develop/worsen geographic atrophy (GA) v Developed/worsend geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.067
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1

Statistical analysis title	Effect of age >50% classic CNV at IVAN entry

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.448
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	2.05

Statistical analysis title	Effect of retinal thickness at IVAN exit(per 10µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.316
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.6

Statistical analysis title	Effect of subretinal fluid (SRF) at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.517
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.46

Statistical analysis title	Effect of PED present at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)

Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.886
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.9

Statistical analysis title	Effect of PED at EFU (at fovea height <85µm)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence[83]
P-value	= 0.003 [84]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.03

Notes:

[83] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[84] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent at fovea)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)

Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence[85]
P-value	= 0.003 [86]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	4.69

Notes:

[85] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[86] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of PED at EFU (absent)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence[87]
P-value	= 0.003 [88]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	6.04

Notes:

[87] - PED categorised:
1: Present at fovea height ≥ 85µm (Reference category)
2: Present at fovea height <85µm
3: Absent at fovea
4: PED absent

[88] - p-value is for overall effect of categorised PED at EFU

Statistical analysis title	Effect of ILMA FE at IVAN exit (ILMA present)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence[89]
P-value	= 0.974 [90]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.24

Notes:

[89] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[90] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of ILMA FE at IVAN exit (no nAMD lesion)

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit

PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
GA in FE at IVAN exit

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence[91]
P-value	= 0.974 [92]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.67

Notes:

[91] - ILMA in FE at IVAN exit categorised:
1: nAMD lesion, ILMA absent (reference category)
2: nAMD lesion, ILMA present
2: No nAMD lesion

[92] - p-value is for overall effect of categorised ILMA in FE at IVAN exit

Statistical analysis title	Effect of GA in FE at IVAN exit

Statistical analysis description:

Multivariable model adjusted for:
Age at IVAN exit (per 10 years)
Gender
Drug and treatment regimen during IVAN trial
Injection rate during EFU (per year)
>50% classic CNV at IVAN entry
Retinal thickness at IVAN exit (per 10µm)
SRF present at IVAN exit
PED present at IVAN exit
PED at EFU (at fovea: height ≥ 85µm, <85µm, PED absent at fovea, PED absent)
ILMA at IVAN exit in FE (nAMD lesion ILMA absent, nAMD lesion ILMA present, No nAMD lesion)

Comparison groups	Developed/worsend geographic atrophy (GA) v Did not develop/worsen geographic atrophy (GA)
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	4.76

Secondary: Low luminance acuity (LLA) in study eye

End point title	Low luminance acuity (LLA) in study eye

End point description:

The association between IVAN treatment allocations and ILMA/GA and LLA was estimated only for attenders because LLA was only measured at the additional research visit. LLA was also not measured during the IVAN trial and therefore these models were not adjusted for baseline values. Sensitivity analyses adjusted for BCVA at IVAN exit visit.

End point type	Secondary

End point timeframe:

Extended follow-up clinic appointment

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	199[93]	105[94]	94[95]	101[96]
Units: Letters				
median (inter-quartile range (Q1-Q3))	38.0 (17.0 to 56.0)	40.0 (18.0 to 56.0)	30.5 (13.0 to 55.0)	31.0 (15.0 to 56.0)

Notes:

[93] - Attenders only

[94] - Attenders only

[95] - Attenders only

[96] - Attenders only

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98[97]	86[98]	113[99]	165[100]
Units: Letters				
median (inter-quartile range (Q1-Q3))	44.0 (20.0 to 55.0)	53.5 (26.0 to 61.0)	27.0 (13.0 to 50.0)	43.0 (20.0 to 57.0)

Notes:

[97] - Attenders only

[98] - Attenders only

[99] - Attenders only

[100] - Attenders only

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34[101]	93[102]	98[103]	28[104]
Units: Letters				
median (inter-quartile range (Q1-Q3))	12.0 (4.0 to 29.0)	27.0 (13.0 to 51.0)	50.5 (26.0 to 60.0)	12.0 (4.0 to 27.5)

Notes:

[101] - Attenders only

[102] - Attenders only

[103] - Attenders only

[104] - Attenders only

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	167[105]			
Units: Letters				
median (inter-quartile range (Q1-Q3))	43.0 (20.0 to 57.0)			

Notes:

[105] - Attenders only

Statistical analyses

Statistical analysis title	Effect of ILMA on LLA

Statistical analysis description:

Linear regression was used to analyse the effect of ILMA in study eyes on low luminance visual acuity at extended follow-up.

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.6
upper limit	-9.4

Statistical analysis title	Effect of GA on LLA

Statistical analysis description:

Linear regression was used to analyse the effect of GA in study eyes on low luminance visual acuity at extended follow-up.

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.6
upper limit	-10.4

Secondary: Low luminance acuity (LLA) in study eye, adjusted for BCVA at IVAN exit (sensitivity analysis)

End point title	Low luminance acuity (LLA) in study eye, adjusted for BCVA at IVAN exit (sensitivity analysis)
End point description:	
Sensitivity analyses adjusting for BCVA at IVAN exit visit.	
End point type	Secondary
End point timeframe:	
Extended follow-up clinic appointment	

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	199[106]	105[107]	94[108]	101[109]
Units: Letters				
median (inter-quartile range (Q1-Q3))	38.0 (17.0 to 56.0)	40.0 (18.0 to 56.0)	30.5 (13.0 to 55.0)	31.0 (15.0 to 56.0)

Notes:

[106] - Attenders only

[107] - Attenders only

[108] - Attenders only

[109] - Attenders only

End point values	IVAN randomised allocation: Discontinuous	Intralesional macular atrophy (ILMA) absent in study eye	Intralesional macular atrophy (ILMA) present in study eye	Geographic atrophy (GA) absent in study eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98[110]	86[111]	113[112]	165[113]
Units: Letters				
median (inter-quartile range (Q1-Q3))	44.0 (20.0 to 55.0)	53.5 (26.0 to 61.0)	27.0 (13.0 to 50.0)	43.0 (20.0 to 57.0)

Notes:
[110] - Attenders only
[111] - Attenders only
[112] - Attenders only
[113] - Attenders only

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34[114]	93[115]	98[116]	28[117]
Units: Letters				
median (inter-quartile range (Q1-Q3))	12.0 (4.0 to 29.0)	27.0 (13.0 to 51.0)	50.5 (26.0 to 60.0)	12.0 (4.0 to 27.5)

Notes:
[114] - Attenders only
[115] - Attenders only
[116] - Attenders only
[117] - Attenders only

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	167[118]			
Units: Letters				
median (inter-quartile range (Q1-Q3))	43.0 (20.0 to 57.0)			

Notes:
[118] - Attenders only

Statistical analyses

Statistical analysis title	Effect of ILMA on LLA
Statistical analysis description:	
Linear regression was used to analyse the effect of ILMA in study eyes on low luminance visual acuity at extended follow-up; adjusting for BCVA at IVAN exit	
Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	-5.3

Statistical analysis title	Effect of GA on LLA
Statistical analysis description:	
Linear regression was used to analyse the effect of ILMA in study eyes on low luminance visual acuity at extended follow-up; adjusting for BCVA at IVAN exit	
Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.4
upper limit	-10.1

Secondary: Quality of life (EQ5D)

End point title	Quality of life (EQ5D)
End point description:	
End point type	Secondary
End point timeframe:	
This analysis was restricted to participants who were willing to compete the EQ-5D-5L and who had data at baseline and follow up.	

End point values	Follow-up cohort	IVAN randomised allocation: Ranibizumab	IVAN randomised allocation: Bevacizumab	IVAN randomised allocation: Continuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	273[119]	147[120]	126[121]	139[122]
Units: EQ5D state score				
median (inter-quartile range (Q1-Q3))	0.8 (0.6 to 0.9)	0.8 (0.6 to 0.9)	0.8 (0.6 to 0.9)	0.8 (0.6 to 0.9)

Notes:

[119] - Exclusions: Participants who did not opt to complete the questionnaire (n=259)

[120] - Exclusions: Participants who did not opt to complete the questionnaire (n=125)

[121] - Exclusions: Participants who did not opt to complete the questionnaire (n=134)

[122] - Exclusions: Participants who did not opt to complete the questionnaire (n=130)

End point values	IVAN randomised allocation:	Intralesional macular atrophy (ILMA)	Intralesional macular atrophy (ILMA)	Geographic atrophy (GA) absent in study

	Discontinuous	absent in study eye	present in study eye	eye
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134[123]	95[124]	172[125]	203[126]
Units: EQ5D state score				
median (inter-quartile range (Q1-Q3))	0.8 (0.6 to 0.9)	0.8 (0.7 to 1.0)	0.7 (0.6 to 0.9)	0.8 (0.6 to 0.9)

Notes:

[123] - Exclusions: Participants who did not opt to complete the questionnaire (n=129)

[124] - Exclusions: Participants who did not opt to complete the questionnaire (n=27)

[125] - Exclusions: Participants who did not opt to complete the questionnaire (n=174)

[126] - Exclusions: Participants who did not opt to complete the questionnaire (n=106)

End point values	Geographic atrophy (GA) present in study eye	Developed/worsened intralesional macular atrophy (ILMA)	Did not develop/worsen intralesional macular atrophy (ILMA)	Developed/worsend geographic atrophy (GA)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64[127]	133[128]	107[129]	53[130]
Units: EQ5D state score				
median (inter-quartile range (Q1-Q3))	0.7 (0.6 to 0.9)	0.7 (0.6 to 0.9)	0.8 (0.7 to 1.0)	0.7 (0.6 to 1.0)

Notes:

[127] - Exclusions: Participants who did not opt to complete the questionnaire (n=95)

[128] - Exclusions: Participants who did not opt to complete the questionnaire (n=110)

[129] - Exclusions: Participants who did not opt to complete the questionnaire (n=31)

[130] - Exclusions: Participants who did not opt to complete the questionnaire (n=89)

End point values	Did not develop/worsen geographic atrophy (GA)			
Subject group type	Reporting group			
Number of subjects analysed	205[131]			
Units: EQ5D state score				
median (inter-quartile range (Q1-Q3))	0.8 (0.6 to 0.9)			

Notes:

[131] - Exclusions: Participants who did not opt to complete the questionnaire (n=106)

Statistical analyses

Statistical analysis title	Effect of trial drug allocation on EQ5D

Statistical analysis description:

For EQ-5D-5L, no transformation could be applied to the data to satisfy the assumptions for linear regression. Therefore, the index score was categorised (EQ-5D-5L score, 1 (no problem in any dimension), 0.80 to 0.99 (a moderate problem in only one dimension), 0.5 to 0.79 (at least two moderate problems in any dimension) and <0.5 (at least one extreme problem)) and ordinal logistic regression was used. These analyses were adjusted for centre size (seven strata as per the IVAN trial).

Comparison groups	IVAN randomised allocation: Ranibizumab v IVAN randomised allocation: Bevacizumab

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2419
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2

Statistical analysis title	Effect of trial treatment regimen on EQ5D

Statistical analysis description:

For EQ-5D-5L, no transformation could be applied to the data to satisfy the assumptions for linear regression. Therefore, the index score was categorised (EQ-5D-5L score, 1 (no problem in any dimension), 0.80 to 0.99 (a moderate problem in only one dimension), 0.5 to 0.79 (at least two moderate problems in any dimension) and <0.5 (at least one extreme problem)) and ordinal logistic regression was used. These analyses were adjusted for centre size (seven strata as per the IVAN trial).

Comparison groups	IVAN randomised allocation: Continuous v IVAN randomised allocation: Discontinuous
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3887
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.3

Statistical analysis title	Effect of ILMA on EQ5D

Statistical analysis description:

For EQ-5D-5L, no transformation could be applied to the data to satisfy the assumptions for linear regression. Therefore, the index score was categorised (EQ-5D-5L score, 1 (no problem in any dimension), 0.80 to 0.99 (a moderate problem in only one dimension), 0.5 to 0.79 (at least two moderate problems in any dimension) and <0.5 (at least one extreme problem)) and ordinal logistic regression was used. These analyses were adjusted for EQ5D score at IVAN exit.

Comparison groups	Intralesional macular atrophy (ILMA) absent in study eye v Intralesional macular atrophy (ILMA) present in study eye

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0413
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1

Statistical analysis title	Effect of GA on EQ5D

Statistical analysis description:

For EQ-5D-5L, no transformation could be applied to the data to satisfy the assumptions for linear regression. Therefore, the index score was categorised (EQ-5D-5L score, 1 (no problem in any dimension), 0.80 to 0.99 (a moderate problem in only one dimension), 0.5 to 0.79 (at least two moderate problems in any dimension) and <0.5 (at least one extreme problem)) and ordinal logistic regression was used. These analyses were adjusted for EQ5D score at IVAN exit.

Comparison groups	Geographic atrophy (GA) absent in study eye v Geographic atrophy (GA) present in study eye
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9794
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for the study began upon completion of the consent form for the clinic appointment until the patient leaves the clinic appointment.

Adverse event reporting additional description:

Only patients who attended a clinic appointment as part of the IVAN follow-up study are included in the adverse events reporting group.

Adverse event that occurred during the clinic appointment were recorded. Any adverse events that occurred between the end of the IVAN trial and consent to the follow-up were considered medical history.

Assessment type	Systematic

Dictionary used

Dictionary name	N/A
Dictionary version	N/A

Reporting groups

Reporting group title	Attenders

Reporting group description: -

Serious adverse events	Attenders		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 199 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Attenders		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 199 (0.50%)		
Eye disorders			
Vitreous floaters	Additional description: This is almost certainly an event that occurred historically but which was noted at the research visit attended by the participant.		
subjects affected / exposed	1 / 199 (0.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2015	SUBSTANTIAL AMENDMENT 1: Section 8 of the protocol (safety reporting) was updated substantially in line with the Sponsor's policy and a table added detailing the terms and definitions of adverse events. New wording was inserted into section 4.4.2 on secondary outcomes explaining that Best Corrected Visual Acuity would be measured with both standard and low luminance visual acuity.
08 March 2016	SUBSTANTIAL AMENDMENT 2: Grounds of Non-Acceptance were received for protocol v5.0 from the MHRA therefore the safety sections were updated further in line with their recommendations and protocol v6.0 was submitted for approval.
21 March 2016	SUBSTANTIAL AMENDMENT 3: A change was made to the Patient Information Leaflet clarifying that research nurses could telephone participants if the reply slip had not been returned after two weeks. The change was made in response to feedback from research nurses and the Macular Disease Society highlighting the importance of verbal communication in this elderly, visually impaired group of participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported