Clinical trial results:
Correlation of functional and structural outcomes with serum antibody profiles in patients with neovascular age-related macular degeneration treated with ranibizumab and healthy subjects: a prospective, controlled monocenter trial

Summary

EudraCT number	2013-003352-20
Trial protocol	DE
Global end of trial date	09 November 2017

Results information

Result version number	v1 (current)
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	469055

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Medical Center of the Johannes Gutenberg - University Mainz
Sponsor organisation address	Langenbeckstraße 2, Mainz, Germany, 55131
Public contact	Clinical Trial Center, University Medical Center of Johannes-Gutenberg University Mainz, +49 6131175741, christina.korb@unimedizin-mainz.de
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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	09 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy (change in BCVA) of IVT administered ranibizumab in subjects with all subtypes of neovascular AMD.

Protection of trial subjects:

The procedures set out in the trial protocol, pertaining to the conduct, evaluation, and documenta-tion of this trial, were designed to ensure that all persons involved in the trial abide by GCP and the ethical principles described in the Declaration of Helsinki. The trial was carried out in keeping with local legal and regulatory requirements.
The requirements of the AMG, the GCP regulation, and the Federal Data Protection Law (BDSG) were adhered to.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 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	Germany: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	6
From 65 to 84 years	49

85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Recruitment and treatment of subjects was performed in one trial center. Eligible trial participants for the AMD group were ≥ 50 years of age, showed subfoveal, juxtafoveal and/or extrafoveal choroidal neovascularisation due to neovascular age-related macular degeneration and had a visual acuity of 20/400 or better in the study eye.

Pre-assignment

Screening details:

71 subjects were enrolled in this study. This comprises 50 patients with neovascular AMD and 20 control subjects. One subject was screened incorrectly and was excluded from the study. 65 subjects completed the trial.

Period 1

Period 1 title	Visit 1 (Baseline)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMD Group (neovascular age-related macular degeneration)

Arm description:

Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.

Arm type	Experimental
Investigational medicinal product name	Lucentis (Ranibizumab, Novartis Pharma GmbH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

Three monthly IVT injections of 0.5mg Lucentis (Ranibizumab), followed by PRN therapy.

Arm title	Control group

Arm description:

Control group of 20 healthy volunteers. Subject received no treatment. Subjects had one visit.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	AMD Group (neovascular age-related macular degeneration)	Control group
Started	50	20
Completed	45	20
Not completed	5	0
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	-

Physician decision	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This Period consist of one visit only and subjects either still participated in the study at this timepoint of not. Therefore, subjects starting and ending the period are equal, whereas subject number in subsequent periods can vary.

Period 2

Period 2 title	Visit 4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMD Group - Visit 4

Arm description:

Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.

Arm type	Experimental
Investigational medicinal product name	Lucentis (Ranibizumab, Novartis Pharma GmbH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

Three monthly IVT injections of 0.5mg Lucentis (Ranibizumab), followed by PRN therapy.

Number of subjects in period 2[2]	AMD Group - Visit 4
Started	49
Completed	49

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: This Period consist of one visit only and subjects either still participated in the study at this timepoint of not. Therefore, subjects starting and ending the period are equal, whereas subject number in subsequent periods can vary.

Period 3

Period 3 title	Visit 7
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMD Group - Visit 7

Arm description:

Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.

Arm type	Experimental
Investigational medicinal product name	Lucentis (Ranibizumab, Novartis Pharma GmbH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

Three monthly IVT injections of 0.5mg Lucentis (Ranibizumab), followed by PRN therapy.

Number of subjects in period 3[3]	AMD Group - Visit 7
Started	45
Completed	45

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: This Period consist of one visit only and subjects either still participated in the study at this timepoint of not. Therefore, subjects starting and ending the period are equal, whereas subject number in subsequent periods can vary.

Baseline characteristics

Reporting groups	
Reporting group title	AMD Group (neovascular age-related macular degeneration)
Reporting group description:	
Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.	
Reporting group title	Control group
Reporting group description:	
Control group of 20 healthy volunteers. Subject received no treatment. Subjects had one visit.	

Reporting group values	AMD Group (neovascular age-related macular degeneration)	Control group	Total
Number of subjects	50	20	70
Age categorical			
Units: Subjects			
Adults (18-64 years)	3	3	6
From 65-84 years	33	16	49
85 years and over	14	1	15
Age continuous			
Units: years			
arithmetic mean	78.48	71.05	
full range (min-max)	58 to 92	50 to 89	-
Gender categorical			
Units: Subjects			
Female	26	15	41
Male	24	5	29
BCVA - ETDRS letters (study eye)			
Visual acuity (VA) was assessed at every study visit. VA measurements were done using the 4 meter Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Best-corrected visual acuity (BCVA) examiners followed the operations manual and training materials by EMMES Corporation. ETDRS letter scores have been measured to monitor the BCVA in patients receiving ranibizumab injections during the study. Reported are the mean values of the ETDRS letter score for each group. VA was not assesed in the control group. The values for the control group were set to 0.			
Units: ETDRS letter score			
arithmetic mean	59.56	0	
standard deviation	± 18.69	± 0	-
Central retinal thickness (CRT)			
Central retinal thickness (CRT) in µm, measured by OCT. CRT was not evalued in the control group. Values for the control group are entered as 0.			
Units: micrometer			
arithmetic mean	414.400	0	
standard deviation	± 109.943	± 0	-
Number of IVT Lucentis injections			
Mean number of IVT ranibizumab injections needed up to Week 24 (Visit 7) in the study eye			
Units: Number			
arithmetic mean	0	0	
full range (min-max)	0 to 0	0 to 0	-
Anti TTR antibody			

Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Transthyretin.			
Units: NFI			
arithmetic mean	329.293044	1566.17808	
standard deviation	± 431.943317	± 6469.5959	-
Anti CA2 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Carbonic anhydrase 2.			
Units: NFI			
arithmetic mean	78920.0649	82277.5998	
standard deviation	± 83062.665	± 137369.877	-
Anti ACO2 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Aconitate hydratase, mitochondrial.			
Units: NFI			
arithmetic mean	421.379196	415.459782	
standard deviation	± 527.218781	± 939.568278	-
Anti HSPD1 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against 60 kDa heat shock protein, mitochondrial.			
Units: NFI			
arithmetic mean	51105.2926	28166.4324	
standard deviation	± 82597.9777	± 28429.8058	-
Anti MBP antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Myelin basic protein.			
Units: NFI			
arithmetic mean	4327.52687	5302.23291	
standard deviation	± 5323.6392	± 15823.628	-
Anti SOD antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Superoxid dismutase.			
Units: NFI			
arithmetic mean	1339.36517	775.195033	
standard deviation	± 2675.99626	± 1965.63135	-
Anti SNCG antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Gamma-synuclein.			
Units: NFI			
arithmetic mean	11879.0444	6843.90305	
standard deviation	± 21368.6767	± 8509.90635	-
Anti ALB antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Albumin.			
Units: NFI			
arithmetic mean	11626.4445	6169.12712	
standard deviation	± 20103.2013	± 12009.731	-
Anti Mucin antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Mucin.			
Units: NFI			
arithmetic mean	2384.57079	4437.92132	
standard deviation	± 2463.19117	± 11389.5247	-
Anti BDNF antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody			

reactivity against Brain-derived neurotrophic factor.			
Units: NFI			
arithmetic mean	20712.2938	27359.6591	
standard deviation	± 35670.3539	± 36640.9169	-
Anti CALR antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Calretuculin.			
Units: NFI			
arithmetic mean	41323.5932	65456.0954	
standard deviation	± 46052.176	± 127619.468	-
Anti NTF3 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Neutrophin-3.			
Units: NFI			
arithmetic mean	23553.6116	56117.993	
standard deviation	± 27445.1585	± 148412.373	-
Anti TF antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Serotransferrin.			
Units: NFI			
arithmetic mean	12805.6082	16308.7444	
standard deviation	± 23422.2683	± 29590.8418	-
Anti OGFR antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Opioid growth factor receptor.			
Units: NFI			
arithmetic mean	4710.51796	6354.39204	
standard deviation	± 6215.37289	± 11293.1811	-
Anti groEL2 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against 60kDa chaperonin 2.			
Units: NFI			
arithmetic mean	45606.0488	25624.7987	
standard deviation	± 75093.5616	± 28341.476	-
Anti NTF4 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Neurotrophin-4.			
Units: NFI			
arithmetic mean	2229.58324	3070.13054	
standard deviation	± 3200.51454	± 6567.93249	-
Anti Dermcidin antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Dermcidin.			
Units: NFI			
arithmetic mean	13639.2395	10111.0475	
standard deviation	± 34467.3342	± 14190.151	-
Anti CLUS antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Clusterin.			
Units: NFI			
arithmetic mean	3613.51411	4695.5411	
standard deviation	± 4544.54803	± 10040.046	-
Anti VEGF antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Vascular endothelial growth factor.			

Units: NFI			
arithmetic mean	5270.56345	7918.14187	
standard deviation	± 10764.55	± 22694.7257	-
Anti EIF4A1 antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Eukaryotic initiation factor 4A-I.			
Units: NFI			
arithmetic mean	1384.61068	1828.40721	
standard deviation	± 2451.61235	± 3855.40767	-
Anti PRKCSH antibody			
Normalized fluorescence intensity obtained by protein microarray measurements of autoantibody reactivity against Glucosidase 2 subunit beta.			
Units: NFI			
arithmetic mean	4092.94729	4280.82021	
standard deviation	± 4680.60189	± 5309.7701	-

End points

End points reporting groups

Reporting group title	AMD Group (neovascular age-related macular degeneration)
Reporting group description:	
Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.	
Reporting group title	Control group
Reporting group description:	
Control group of 20 healthy volunteers. Subject received no treatment. Subjects had one visit.	
Reporting group title	AMD Group - Visit 4
Reporting group description:	
Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.	
Reporting group title	AMD Group - Visit 7
Reporting group description:	
Patients in the AMD group received three IVT Lucentis injections (0.5mg) within the first three months, followed by an individual therapy based on clinical progress (pro re nata, PRN). Patients had a total of six visits.	

Primary: Change from Baseline (visit 1) in BCVA (ETDRS letter score) at Week 12 (visit 4) in the study eye

End point title	Change from Baseline (visit 1) in BCVA (ETDRS letter score) at Week 12 (visit 4) in the study eye[1]
End point description:	
The study was designed to assess the efficacy of IVT administered ranibizumab in subjects with all subtypes of neovascular AMD. The primary endpoint is the analysis of changes in BCVA, evaluated by ETDRS scores, from baseline (visit 1) to week 12 (visit 4). Regarding the ETDRS scores of all AMD patients, a significant increase in the BCVA can be observed in week 12 after study begin. At the start point of the study, the mean ETDRS letter score of the study population was at 59.347. After 12 weeks of Lucentis treatment, the score increased to 62.939. Treated patients gained 3.6 letters on average.	
End point type	Primary
End point timeframe:	
Baseline (visit 1) to week 12 (visit 4)	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: BCVA was not assessed in the control group.	

End point values	AMD Group (neovascular age-related macular degeneration)	AMD Group - Visit 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: ETDRS letter score				
arithmetic mean (standard deviation)	59.347 (± 18.820)	62.939 (± 18.431)		

Statistical analyses

Statistical analysis title	AMD group V1 vs V4
Comparison groups	AMD Group (neovascular age-related macular degeneration) v AMD Group - Visit 4
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005
Method	Paired two-sided t test

Secondary: Change from Baseline (visit 1) in BCVA (ETDRS letter score) at Week 24 (visit 7) in the study eye

End point title	Change from Baseline (visit 1) in BCVA (ETDRS letter score) at Week 24 (visit 7) in the study eye[2]

End point description:

The secondary endpoints included the analysis of changes in BCVA from baseline (visit 1) to week 24 (visit 7). The mean ETDRS letter score of all AMD patients treated with ranibizumab increased from 59.444 to 62.911, but this ef-fect could not reach the .05 level for significance.

End point type	Secondary

End point timeframe:

Baseline (visit 1) to week 24 (visit 7).

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: BCVA was not assessed in the control group.

End point values	AMD Group (neovascular age-related macular degeneration)	AMD Group - Visit 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: ETDRS letter score				
arithmetic mean (standard deviation)	59.444 (± 18.555)	62.911 (± 20.020)		

Statistical analyses

Statistical analysis title	paired t test
Comparison groups	AMD Group (neovascular age-related macular degeneration) v AMD Group - Visit 7

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.11
Method	Paired two sided t test

Secondary: Absolute change from baseline (visit 1) in central retinal thickness at week 24 (visit 7)

End point title	Absolute change from baseline (visit 1) in central retinal thickness at week 24 (visit 7)[3]

End point description:

The absolute change from baseline (visit 1) in central retinal thickness at week 24 (visit 7) in the study eye was assesed. Changes in central retinal thickness (CRT) in the study population were analysed by OCT. CRT values of V1 and V7 were compared by two-sided paired t test. CRT measured in the complete AMD study population was significantly (p<0.001) decreased at week 24 compared to the baseline measurement. The mean CRT dropped from 393.4µm to 296.8µm.

End point type	Secondary

End point timeframe:

Baseline (visit 1) to week 24 (visit 7).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Central retinal thickness was not assessed in the control group.

End point values	AMD Group (neovascular age-related macular degeneration)	AMD Group - Visit 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: micrometer				
arithmetic mean (standard deviation)	393.400 (± 109.170)	296.822 (± 75.659)		

Statistical analyses

Statistical analysis title	paired t test
Comparison groups	AMD Group (neovascular age-related macular degeneration) v AMD Group - Visit 7
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Paired two sided t test

Secondary: Mean number of IVT ranibizumab injections

End point title	Mean number of IVT ranibizumab injections

End point description:	
The mean number of IVT ranibizumab injections in the AMD group is 4.956	
End point type	Secondary
End point timeframe:	
Baseline (visit 1) to week 24 (visit 7)	

End point values	AMD Group - Visit 7			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Count				
number (not applicable)	4.956			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in anti TTR levels

End point title	Change in anti TTR levels
End point description:	
Relative changes in serological autoantibody levels to TTR.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	329.293044 (± 431.943317)	1566.17808 (± 6469.5959)	589.946731 (± 841.376927)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in anti CA2 levels

End point title	Change in anti CA2 levels

End point description:

Relative changes in serological autoantibody levels to TTR.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	78920.0649 (± 83062.665)	82277.5998 (± 137369.877)	131123.099 (± 137131.564)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ACO2 antibodies

End point title	Change in ACO2 antibodies

End point description:

Relative changes in serological autoantibody levels to ACO2.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	421.379196 (± 527.218781)	415.459782 (± 939.568278)	705.688399 (± 975.255285)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HSPD1 antibodies

End point title	Change in HSPD1 antibodies

End point description:

Relative changes in serological autoantibody levels to HSPD1.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	51105.2926 (± 82597.9777)	28166.4324 (± 28429.8058)	90819.3211 (± 144238.578)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MBP antibodies

End point title	Change in MBP antibodies

End point description:

Relative changes in serological autoantibody levels to MBP.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	4327.52687 (± 5323.6392)	5302.23291 (± 15823.628)	11874.9915 (± 28818.5154)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SOD antibodies

End point title	Change in SOD antibodies
End point description:	
Relative changes in serological autoantibody levels to SOD.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	1339.36517 (± 2675.99626)	775.195033 (± 1965.63135)	1950.46017 (± 4314.98206)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SNCG antibodies

End point title	Change in SNCG antibodies
End point description:	
Relative changes in serological autoantibody levels to SNCG.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	11879.0444 (± 21368.6767)	6843.90305 (± 8509.90635)	15918.4531 (± 30303.8745)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ALB antibodies

End point title	Change in ALB antibodies
End point description: Relative changes in serological autoantibody levels to ALB.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	11626.4445 (± 20103.2013)	6169.12712 (± 12009.731)	21660.8042 (± 55524.1703)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Mucin antibodies

End point title	Change in Mucin antibodies
End point description: Relative changes in serological autoantibody levels to Mucin 5B.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	2384.57079 (± 2463.19117)	4437.92132 (± 11389.5247)	5710.1092 (± 7395.27252)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BDNF antibodies

End point title	Change in BDNF antibodies

End point description:

Relative changes in serological autoantibody levels to BDNF.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	20712.2938 (± 35670.3539)	27359.6591 (± 36640.9169)	38896.7629 (± 86988.8332)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CALR antibodies

End point title	Change in CALR antibodies

End point description:

Relative changes in serological autoantibody levels to CALR.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	41323.5932 (± 46052.176)	65456.0954 (± 127619.468)	88559.5047 (± 128164.807)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NTF3 antibodies

End point title	Change in NTF3 antibodies
End point description: Relative changes in serological autoantibody levels to NTF3.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	23553.6116 (± 27445.1585)	56117.993 (± 148412.373)	60781.7721 (± 81896.6784)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in TF antibodies

End point title	Change in TF antibodies
End point description: Relative changes in serological autoantibody levels to TF.	
End point type	Secondary

End point timeframe:
24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	12805.6082 (± 23422.2683)	16308.7444 (± 29590.8418)	32491.9646 (± 55884.5263)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in OGFR antibodies

End point title	Change in OGFR antibodies
End point description: Relative changes in serological autoantibody levels to OGFR.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	4710.51796 (± 6215.37289)	6354.39204 (± 11293.1811)	13931.4798 (± 38234.8327)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in groEL2 antibodies

End point title	Change in groEL2 antibodies

End point description: Relative changes in serological autoantibody levels to groEL2.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	45606.0488 (± 75093.5616)	25624.7987 (± 28341.476)	78762.2063 (± 117962.448)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NTF4 antibodies

End point title	Change in NTF4 antibodies
End point description: Relative changes in serological autoantibody levels to NTF4.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	2229.58324 (± 3200.51454)	3070.13054 (± 6567.93249)	4857.94573 (± 6272.06139)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Dermcidin antibodies

End point title	Change in Dermcidin antibodies

End point description:

Relative changes in serological autoantibody levels to Dermcidin.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	13639.2395 (± 34467.3342)	10111.0475 (± 14190.151)	19040.8268 (± 20508.2208)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CLUS antibodies

End point title	Change in CLUS antibodies

End point description:

Relative changes in serological autoantibody levels to CLUS.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	3613.51411 (± 4544.54803)	4695.5411 (± 10040.046)	9231.28756 (± 11712.3194)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VEGF antibodies

End point title	Change in VEGF antibodies
End point description:	
Relative changes in serological autoantibody levels to VEGF.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	5270.56345 (± 10764.55)	7918.14187 (± 22694.7257)	13302.2931 (± 17108.5068)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EIF4A1 antibodies

End point title	Change in EIF4A1 antibodies
End point description:	
Relative changes in serological autoantibody levels to EIF4A1.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	1384.61068 (± 2451.61235)	1828.40721 (± 3855.40767)	3028.33669 (± 6104.8793)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PRKCSH antibodies

End point title	Change in PRKCSH antibodies

End point description:

Relative changes in serological autoantibody levels to PRKCSH.

End point type	Secondary

End point timeframe:

24 weeks

End point values	AMD Group (neovascular age-related macular degeneration)	Control group	AMD Group - Visit 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	20	45	
Units: NFI				
arithmetic mean (standard deviation)	4092.94729 (± 4680.60189)	4280.82021 (± 5309.7701)	8881.44175 (± 20014.9407)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
24 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	AMD Group
Reporting group description:	
AMD Group receiving three Lucentis injections (0.5mg) within the first three months, followed by individual therapy interval based on the clinical progress (pro re nata, PRN).	

Serious adverse events	AMD Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Traumatic arthrosis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				
Inguinal hernia				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchial haemorrhage				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Device related infection				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Osteomyelitis				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
alternative dictionary used: MedDRA 20.0				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Product issues			
Device loosening			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AMD Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 50 (74.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye naevus			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Skin papilloma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

Hypertension			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Fibrosis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Sensation of foreign body			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Prostatitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Investigations			

Intraocular pressure increased subjects affected / exposed occurrences (all) Serum ferritin decreased subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2 1 / 50 (2.00%) 1		
Injury, poisoning and procedural complications Accident subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Patella fracture subjects affected / exposed occurrences (all) Skin laceration subjects affected / exposed occurrences (all)	 1 / 50 (2.00%) 1 1 / 50 (2.00%) 1 2 / 50 (4.00%) 2 1 / 50 (2.00%) 1 1 / 50 (2.00%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	 1 / 50 (2.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Neuritis subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 4 1 / 50 (2.00%) 1		
Ear and labyrinth disorders Vertigo			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Cataract			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Chalazion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Conjunctival haemorrhage			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Corneal erosion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Detachment of retinal pigment epithelium			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Exfoliation syndrome			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye haematoma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Macular cyst			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Macular oedema			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Neovascular age-related macular degeneration			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Ocular hyperaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Retinal pigment epithelial tear			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Retinal pigment epitheliopathy			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Subretinal fluid			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	1		
Trichiasis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Visual acuity reduced			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Vitreous detachment			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Vitreous disorder			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Cystitis			

subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Gingivitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported