Clinical trial results:
Wirksamkeit von Ranibizumab bei Patienten mit CHORIOIDALER NEOVASKULARISATION (CNV), als Folge einer altersbedingten Makuladegeneration (AMD), bei einer Gabe alle zwei Monate gegenüber der Behandlung bei Bedarf

Efficacy of Ranibizumab Treatment Every 2 Month Compared to Treatment on Demand on Patients With Choroidal Neo-vascularization (CNV) as a Consequence of Age-related Macular Degeneration (AMD) [ClinicalTrials.gov]

Efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with neovascular age-related macular degeneration - RABIMO trial [Paper 2017]

Summary

EudraCT number	2009-017324-11
Trial protocol	DE
Global end of trial date	06 August 2013
Results information	
Result version number	v1 (current)
This version publication date	05 November 2021
First version publication date	05 November 2021
Summary attachment (see zip file)	Summary results (RABIMO_O-1019_01-2-0-56C556-20131119101056.pdf)

Trial information

Trial identification	
Sponsor protocol code	CRFB002ADE09T
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01831947
WHO universal trial number (UTN)	-
Other trial identifiers	RABIMO: IFS-218

Notes:

Sponsors	
Sponsor organisation name	Universitätsmedizin Göttingen (UMG), Georg-August-Universität Göttingen Stiftung Öffentlichen Rechts
Sponsor organisation address	Robert-Koch-Straße 40, Göttingen, Germany, 37075
Public contact	Studienzentrum UMG, Universitätsmedizin Göttingen (UMG), +49 5513960812, sz-umg.sponsor-qm@med.uni-goettingen.de

Scientific contact	Prof. Dr. Hans Michael Hoerauf, Klinik für Augenheilkunde, Universitätsmedizin Göttingen (UMG), +49 5513963580, augenklinik@med.uni-goettingen.de

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	10 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2013
Global end of trial reached?	Yes
Global end of trial date	06 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Ziel der klinischen Prüfung ist die Überprüfung des Einflusses von intravitreal injiziertem Ranibizumab in unterschiedlichen Intervallen auf die Sehschärfe von Patienten mit neovaskulärer CNV im Rahmen einer AMD. Dabei erhalten alle Patienten zunächst 3 Injektionen in monatlichem Abstand und im weiteren Verlauf entweder 2-monatlich als fixes Schema oder lediglich bei Befundverschlechterung („on demand—).

Evaluation prospectively the efficacy and safety of a fixed bimonthly ranibizumab treatment regimen (RABIMO) in eyes with neovascular age-related macular degeneration (nAMD) and comparison of results with a pro re nata (PRN) treatment scheme.

Impact of injection frequency of ranibizumab on visual acuity development /
BCVA - best corrected visual acuity after 12 months in comparison to baseline / ...[Paper 2017]

Protection of trial subjects:

To minimize the risk of AMD worsening in all patients, monthly assessments were introduced to identify patients for whom bi-monthly injection intervals were inadequate. [Dissertation 2017]

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2010
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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	1
From 65 to 84 years	29
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 12 months /
First patient in: 28.04.2010 /
Last patient in: 29.03.2012

Pre-assignment

Screening details:

Inclusion and exclusion criteria / Demographic data / Medical history / Concomitant diseases / Physical examination and vital signs / Blood count / Visual acuity / Ophthalmological examination / Optical coherence tomography (OCT) / Fundus photography Fluorescein angiography / Accompanying medication / Tonometry

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RABIMO group (randomized)

Arm description:

Experimental: Ranibizumab fixed dose / fixed bimonthly ranibizumab treatment regimen (RABIMO) / Injection of 0.5 mg Ranibizumab every 2 months for one year, following a monthly injection during the first 3 months.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection

Dosage and administration details:

Ranibizumab 0.5 mg, eight injections
After three initial monthly injections, patients were randomised to receive ranibizumab bimonthly.

Arm title	PRN group (randomized)

Arm description:

Experimental: Ranibizumab on demand / pro re nata (PRN) treatment scheme /
Injection of 0.5 mg Ranibizumab on demand for one year, following a monthly injection during the first 3 months.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection

Dosage and administration details:

0.5 mg/eye, intravitreal injection

Number of subjects in period 1	RABIMO group (randomized)	PRN group (randomized)
Started	19	20
Completed	18	15
Not completed	1	5
Adverse event, serious fatal	1	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial (overall period)

Reporting group description: -

Reporting group values	overall trial (overall period)	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	29	29	
85 years and over	9	9	
Gender categorical Units: Subjects			
Female	25	25	
Male	14	14	

End points

End points reporting groups

Reporting group title	RABIMO group (randomized)
Reporting group description:	
Experimental: Ranibizumab fixed dose / fixed bimonthly ranibizumab treatment regimen (RABIMO) / Injection of 0.5 mg Ranibizumab every 2 months for one year, following a monthly injection during the first 3 months.	
Reporting group title	PRN group (randomized)
Reporting group description:	
Experimental: Ranibizumab on demand / pro re nata (PRN) treatment scheme / Injection of 0.5 mg Ranibizumab on demand for one year, following a monthly injection during the first 3 months.	

Primary: BCVA: best-corrected visual acuity

End point title	BCVA: best-corrected visual acuity
End point description:	
Impact of injection frequency on visual acuity development (best-corrected visual acuity (BCVA) after 12 months in comparison to baseline.	
End point type	Primary
End point timeframe:	
after 12 months (in comparison to baseline)	

End point values	RABIMO group (randomized)	PRN group (randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[1]	20[2]		
Units: interquartile range (IQR)				
median (inter-quartile range (Q1-Q3))				
significant difference in BCVA	6.5 (4 to 19)	9 (0.5 to 15.5)		

Notes:

[1] - fixed-dose / RABIMO group

[2] - pro re nata (as needed) / PRN group

Attachments (see zip file)	Median (IQR) BCVA.jpg

Statistical analyses

Statistical analysis title	intention to treat (ITT)
Statistical analysis description:	
non-inferiority design	
Comparison groups	PRN group (randomized) v RABIMO group (randomized)

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	t-test, 1-sided
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard deviation

Notes:

[3] - non-inferiority design for the difference μB-μ2 /

μB: expected value in "on-demand" group /
μ2: expected value in "fixed dose" group /

difference between 12-month visit (visit 14) and baseline visit, under therapy
μ2 denotes the fixed 2-month injection
[4] - one-sided t-test (alpha = 5%) on the ITT

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded during the entire study period.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD-10
Dictionary version	2019

Reporting groups

Reporting group title	PRN group
Reporting group description: -	
Reporting group title	RABIMO group

Reporting group description: -

Serious adverse events	PRN group	RABIMO group	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)	6 / 19 (31.58%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	2	1	
Vascular disorders			
Benigne essential hypertension	Additional description: 577		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke, not specified as haemorrhage or infarction	Additional description: 740 (Dysphasia and aphasia), sudden cardiac Death		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal aortic aneurysm, without mention of rupture	Additional description: 741		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atherosclerosis of arteries of extremities	Additional description: 545 (left leg)		

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Mitral (valve) insufficiency	Additional description: 573 (Paroxysmal atrial fibrillation)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Acquired absence of leg at or below knee	Additional description: 572 (left site, amputation)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Other transient cerebral ischaemic attacks and related syndromes	Additional description: 598		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphocyte-rich (classical) Hodgkin lymphoma	Additional description: 257, Relapse M. Hodgkin		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma	Additional description: 801 (Diffuse follicle centre lymphoma)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Other ill-defined and unspecified causes of mortality	Additional description: 1063, Other ill-defined and unspecified causes of mortality, Death		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			

Retinal haemorrhage	Additional description: 1044		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Degeneration of macula and posterior pole	Additional description: 1185, 1186 (both 218_0001)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocolitis due to Clostridium difficile	Additional description: 547		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture of pubis	Additional description: 537		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis of vertebra	Additional description: 497, cervical, Discitis, unspecified (spondylodiscitis V2-3, V3-4)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyogenic arthritis, unspecified	Additional description: 550 (knee)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza, virus not identified	Additional description: 943, severe infection, (Urinary tract infection, site not specified)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis due to adenovirus	Additional description: 417 worsening of infectious keratitis		

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic Inflammatory Response Syndrome of infectious origin with organ failure	Additional description: 599, Septic shock, Cardiac arrest, unspecified, Death		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope and collapse	Additional description: 922 (Other infectious diseases)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	PRN group	RABIMO group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)	13 / 19 (68.42%)	
Vascular disorders			
Essential (primary) hypertension	Additional description: 297, 546 progression) (both 218_0002)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	2	
Cardiac disorders			
Paroxysmal atrial fibrillation	Additional description: 700 (tachycardiac arrhythmia)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Restlessness and agitation	Additional description: 1123		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Other iron deficiency anaemias	Additional description: 1205		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Eye disorders			

Blepharitis	Additional description: 1046, 1083, 1045, 1047, 1165		
subjects affected / exposed	2 / 20 (10.00%)	3 / 19 (15.79%)	
occurrences (all)	2	3	
Conjunctival haemorrhage	Additional description: 1043 (up, resorption), 1064, 1042 (down, temporal)		
subjects affected / exposed	2 / 20 (10.00%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Corneal ulcer	Additional description: 538		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hereditary corneal dystrophies	Additional description: 781		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Other disorders of choroid	Additional description: 983		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Degeneration of macula and posterior pole	Additional description: 842		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Other degeneration of macula and posterior pole	Additional description: 822		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Peripheral retinal degeneration	Additional description: 862 (defects)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Separation of retinal layers	Additional description: 982 (RPE seperation)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Retinal disorder, unspecified	Additional description: 1103 (RPE abnormalities, down)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Other vitreous opacities	Additional description: 823, 942, 1166		
subjects affected / exposed	0 / 20 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Ocular pain	Additional description: 551		

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion, not elsewhere classified			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Cough	Additional description: 1003 (after fluorescence angiography)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Other depressive episodes	Additional description: 882		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Endocrine disorders			
Generalized hyperhidrosis	Additional description: 883, Ectopic hormone secretion, not elsewhere classified (increased sweating / hormones liver)		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Other dorsalgia	Additional description: 457, 802		
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Osseous and subluxation stenosis of intervertebral foramina	Additional description: 1023		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Localized oedema	Additional description: 517 (Ankle, both sides)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Fracture of thoracic vertebra	Additional description: 660 (thoracic vertebra 12)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Injury of Achilles tendon	Additional description: 541 (left site)		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Zoster without complication	Additional description: 1022		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
nasopharyngitis [common cold]	Additional description: 574, 600, 1002		
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Acute upper respiratory infections of multiple and unspecified sites	Additional description: 620		
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pneumonia, unspecified	Additional description: 720		
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Bronchitis, not specified as acute or chronic	Additional description: 761, 544, 640		
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2010	Protocol Version 1.3 and ICF modification

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28102456