Clinical trial results:
Evaluation of an additional therapeutic approach to diabetic macular edema by combining standard therapy (intravitreal injection of a VEGF inhibitor) with micropulse diode laser treatment in a randomized, controlled proof of concept study

Summary

EudraCT number	2013-003056-21
Trial protocol	DE
Global end of trial date	13 December 2016

Results information

Result version number	v1 (current)
This version publication date	22 August 2021
First version publication date	22 August 2021

Trial information

Trial identification

Sponsor protocol code	ReCaLL-2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02059772
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GWT-TUD GmbH
Sponsor organisation address	Freiberger Str. 33, Dresden, Germany, 01067
Public contact	Medical Consulting, GWT-TUD GmbH, 0049 351 25933 100, medical.consulting@g-wt.de
Scientific contact	Prof. Dr. Katrin Engelmann, Klinikum Chemnitz gGmbH Klinik für Augenheilkunde Flemmingstraße 2 09116 Chemnitz, 0049 371 333 33230, k.engelmann@skc.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	29 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2016
Global end of trial reached?	Yes
Global end of trial date	13 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate if a combination therapy with micropulse diode laser treatment shows non-inferiority on visual acuity within 12 months in comparison to standard therapy (intravitreal injection of ranibizumab only) as measured by best corrected visual acuity (BCVA)

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study was also be carried out in keeping with applicable local law(s) and regulation(s).
In the framework of the clinical study no increased risk for side effects or complications were expected as compared to the daily used standard medical care in the treatment of diabetic macular edemabecause (DME) no irreversible structural damage of the retina has been seen so far after micropulse diode laser therapy.
Dosage and frequency of Lucentis® treatment applied in this study followed the specifications given in the SmPC as well as the standard medical recommended by
German Ophthalmological Society (DOG).

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	30 April 2014
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: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	8
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 30th April 2014 and 13th December 2016, a total of 25 patients were included in the study at one study site in Germany. Of them, 4 patients were screening failures. The study was prematurely terminated due to significant delay in the patient recruitment which did not expect completion of the study in a reasonable time frame.

Pre-assignment

Screening details:

21 subjects entered the upload phase. 2 subjects dropped-out during the upload phase, 1 due to an AE and 1 withdrew the consent. The remaining 19 subjects were randomized to one of the two treatment groups: 9 patients to Group A and 10 patients to Group B.

Pre-assignment period milestones

Number of subjects started	21
Number of subjects completed	19

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A - Control Group

Arm description:

During the treatment phase (Visit 5 to 13) subjects received standard therapy with intravitreal injections of Lucentis® according to SmPC until stable visual acuity was achieved. If retreatment criteria were met, follow-up injections of Lucentis® were given until stability of best corrected visual acuity (BCVA) was reached again.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Dose/route: single intravitreal injection of 0.5 mg ranibizumab
Frequency: one single injection every 4 weeks as necessary up to a maximum of 12 injections in total (Visit 5 to 13)

Arm title	Group B - Treatment Group

Arm description:

During the treatment phase (Visit 5 to 13) subjects received standard therapy with intravitreal injections of Lucentis® according to SmPC until stable visual acuity was achieved. If retreatment criteria were met, follow-up injections of Lucentis® were given until stability of BCVA was reached again. Patients in Arm B additionally received two treatments with the micropulse diode laser, one at Visit 5 and one at Visit 6.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Dose/route: single intravitreal injection of 0.5 mg ranibizumab
Frequency: one single injection every 4 weeks as necessary up to a maximum of 12 injections in total (Visit 5 to 13)

Number of subjects in period 1[1]	Group A - Control Group	Group B - Treatment Group
Started	9	10
Completed	7	10
Not completed	2	0
Adverse event, non-fatal	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: 21 patients were enrolled into the up-load phase and received intravitreal injections of Lucentis®. Since only 19 patients received 3 consecutive intravitreal injections of Lucentis® in intervals of 4 weeks only these were randomized into one of two study arms.

Baseline characteristics

Reporting groups	
Reporting group title	Group A - Control Group
Reporting group description:	
During the treatment phase (Visit 5 to 13) subjects received standard therapy with intravitreal injections of Lucentis® according to SmPC until stable visual acuity was achieved. If retreatment criteria were met, follow-up injections of Lucentis® were given until stability of best corrected visual acuity (BCVA) was reached again.	
Reporting group title	Group B - Treatment Group
Reporting group description:	
During the treatment phase (Visit 5 to 13) subjects received standard therapy with intravitreal injections of Lucentis® according to SmPC until stable visual acuity was achieved. If retreatment criteria were met, follow-up injections of Lucentis® were given until stability of BCVA was reached again. Patients in Arm B additionally received two treatments with the micropulse diode laser, one at Visit 5 and one at Visit 6.	

Reporting group values	Group A - Control Group	Group B - Treatment Group	Total
Number of subjects	9	10	19
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	3	6
From 65-84 years	6	7	13
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	70.78	70.70	
standard deviation	± 8.96	± 7.60	-
Gender categorical Units: Subjects			
Female	3	2	5
Male	6	8	14

End points

End points reporting groups

Reporting group title	Group A - Control Group

Reporting group description:

During the treatment phase (Visit 5 to 13) subjects received standard therapy with intravitreal injections of Lucentis® according to SmPC until stable visual acuity was achieved. If retreatment criteria were met, follow-up injections of Lucentis® were given until stability of best corrected visual acuity (BCVA) was reached again.

Reporting group title	Group B - Treatment Group

Reporting group description:

During the treatment phase (Visit 5 to 13) subjects received standard therapy with intravitreal injections of Lucentis® according to SmPC until stable visual acuity was achieved. If retreatment criteria were met, follow-up injections of Lucentis® were given until stability of BCVA was reached again. Patients in Arm B additionally received two treatments with the micropulse diode laser, one at Visit 5 and one at Visit 6.

Primary: Change in best corrected visual acuity (BCVA)

End point title	Change in best corrected visual acuity (BCVA)

End point description:

The primary variable of this study was the mean average change in BCVA over 12 months using an ETDRS visual acuity test.

End point type	Primary

End point timeframe:

over 12 month

End point values	Group A - Control Group	Group B - Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: ETDRS-charts				
arithmetic mean (standard deviation)	5.86 (± 1.86)	9.30 (± 5.12)		

Statistical analyses

Statistical analysis title	Inter-group comparison of change in BCVA

Statistical analysis description:

In the present study, non-inferiority of Arm B (treatment group) was evaluated and compared to Arm A (control group). Statistical test hypotheses were: H0: μArmB − μArmA ≤ -d / H1: μArmB − μArmA > -d The non-inferiority limit was set to d = 0.064 (based on a 20% difference of a baseline score μBCVA = 0.32) and the standard deviation of outcome was estimated conservatively with σ = 0.07.

Comparison groups	Group B - Treatment Group v Group A - Control Group

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.075
Method	Student´s t-test independent

Notes:

[1] - Primary target analysis for non-inferiority was based on a one-sided 5% significance level referring to the stated direction in the statistical hypotheses.

Secondary: Change in CMT

End point title	Change in CMT

End point description:

The secondary variables were the mean average change in CMT over 12 months as measured by SD-OCT and the number of intravitreal injections with Lucentis®.

End point type	Secondary

End point timeframe:

over 12 month

End point values	Group A - Control Group	Group B - Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: SD-OCT				
arithmetic mean (standard deviation)	-104.86 (± 68.76)	-124.50 (± 81.08)		

Statistical analyses

Statistical analysis title	Inter-group comparison of change in CMT (µm)
Comparison groups	Group A - Control Group v Group B - Treatment Group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.609
Method	Student´s t-test independent

Secondary: Number of ranibizumab injections

End point title	Number of ranibizumab injections

End point description:

Intravitreal Lucentis® injections were administered 3 times during the upload period and afterwards only when criteria for retreatment were given. Thus, the number of injections
should have varied between 3 and 12.
For evaluation of the group difference, the proportion of subjects who received treatment with Lucentis per visit and group was calculated and cumulated. Data demonstrate that subjects in Group B received less injections with Lucentis than subjects in Group A (in the PPS on average 9 injections per patient in Group A and 7.5 in Group B over a period of 12 months).

End point type	Secondary

End point timeframe:

over 12 month

End point values	Group A - Control Group	Group B - Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: injections per subject	36	60		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The observation phase for AEs started with signing the informed consent form and ended in general with the last visit of follow-up (over 12 month).

Adverse event reporting additional description:

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the subject were documented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Treament phase

Reporting group description: -

Serious adverse events	Treament phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 19 (36.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Apoplexy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart attack			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asystole			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Stent implantation			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope of unknown origin			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Orchitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected left toe (big)			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic foot open			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treament phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 19 (68.42%)		
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
Erosio cornae			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Vitreous prolapse			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Occular redness, intraocular pressure			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea, diarrhea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Infections and infestations			
Common cold			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Diabetic foot open			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vocal cord inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2014	The study was conducted according to the approved study protocol Version 2.0, dated 26.02.2014. An amendment resulting in Version 3.0, dated 09.12.2014, was issued to reflect the change of the Principal Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The reason for early termination of enrollment was a substantial delay in recruitment which did not suggest completion of the study in a reasonable time frame.

Notes: