# 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<br>Klinik für Augenheilkunde<br>Flemmingstraße 2<br>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<br>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<br>Units: years | | | |
| arithmetic mean | 70.78 | 70.70 | |
| standard deviation | ± 8.96 | ± 7.60 | - |
| Gender categorical<br>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<br>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: