# Clinical trial results:
# A randomized, double-masked study with intraocular bevacizumab (Avastin®) compared with intraocular triamcinolone (Volon A®) in patients with clinical significant diabetic macular edema

## Summary

| | |
|---|---|
| EudraCT number | 2007-001553-26 |
| Trial protocol | AT |
| Global end of trial date | 29 July 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 June 2021 |
| First version publication date | 12 June 2021 |
| Summary attachment (see zip file) | Intravitreal bevacizumab (Avastin) versus triamcinolone (Volon A) for treatment of diabetic macular edema: one-year results (eye2013242a.pdf)<br>Detailed analysis of retinal morphology in patients with diabetic macular edema (DME) randomized to ranibizumab or triamcinolone treatment (417_2017_Article_3828.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | Protocol 03_10_2007 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00682539 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Medical University Vienna |
| Sponsor organisation address | Waehringerguertel 18-20, Vienna, Austria, 1090 |
| Public contact | Clinical Trial Center, Department of Ophthalmology and Optometry, +43 1 4040048470, eye-studies@meduniwien.ac.at |
| Scientific contact | Clinical Trial Center, Department of Ophthalmology and Optometry, +43 1 4040048470, eye-studies@meduniwien.ac.at |

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 July 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Primary objectives:
Evaluation of efficacy of the treatment with intravitreal administered injections of Bevacizumab (Avastin®) compared with Triamcinolone (Volon A®) in patients with clinical significant diabetic macular edema. The main focus of the assessments of efficacy is:
1. The percent change in macular edema measured with standard optical coherence tomography (OCT).
2. The absolute change in visual acuity analyzed by standardized charts according to the protocol used in the Early Retreatment in Diabetic Retinopathy Study (ETDRS).

Protection of trial subjects:

The trial followed the tenets of the Helsinki Declaration. Before study inclusion, the interventional study design and examinations for scientific purposes were explained to each patient in a personal interview and informed consent was obtained. Contact information of the study team was provided. Intravitreal injections were administered in local anaesthesia. Lubricant eye drops were used against eye-discomfort after the injection. Patients

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 November 2007 |
| 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 | Austria: 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) | 44 |
| From 65 to 84 years | 27 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study patients were recruited between 2007 and 2014 at the outpatient clinic of the Department of Ophthalmology, Medical University Vienna, Austria.

### Pre-assignment

Screening details:

Only one eye of each patient could be included in the study. Eligibility criteria were patients aged ≥18 years with type 1 or 2 diabetes, a best-corrected visual acuity (BCVA) between 20/25 and 20/400 (Snellen equivalent) and a macula center involving DME with a CRT of more than 300 µm measured with spectral domain (SD) OCT.

### Period 1

| | |
|---|---|
| Period 1 title | Bevacizumab vs Triamcinolone |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Carer |

Blinding implementation details:

There were two teams of study investigators: Investigators examining the patients were masked to treatment arm. Investigators applying the medication were masked to study results. Since Triamcinolone was injected no more than every three months sham injections were given intermittend to maintain patient masking.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Bevacizumab |

Arm description:

After a loading dose of three monthly injections of 2.5mg Avastin, PRN treatment based on predefined morphological and functional retreatment criteria, that were reassessed monthly.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intraocular use |

Dosage and administration details:

Avolume of 0.1 ml containing 2.5mg bevacizumab (Avastin, Roche Pharma AG) was injected at 3.5mm distance from the limbus through the inferotemporal pars plana.

| | |
|---|---|
| **Arm title** | Triamcinolone |

Arm description:

15 patients with a clinical significant diabetic macular edema receive an intraocular injection of 8mg triamcinolone at baseline under sterile conditions. 1 and 2 month after the baseline injection, patients receive a sham injection. After three month re-injection of 8mg Triamcinolone is performed as needed following a predefined protocol. In between two injection of 8mg Triamcinolone must be an temporal interval of at least 3 months.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Triamcinolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intraocular use |

Dosage and administration details:

Avolume of 0.1 ml containing 8mg triamcinolone (Volon A, Dermapharm GmbH) was injected at 3.5mm distance from the limbus through the inferotemporal pars plana.

| **Number of subjects in period 1[1]** | Bevacizumab | Triamcinolone |
|---|---|---|
| Started | 18 | 16 |
| Completed | 15 | 15 |
| Not completed | 3 | 1 |
| Lost to follow-up | 3 | 1 |

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: The first period was a comparison between bevacizumab and triamcinolone. The second period was a comparison between ranibizumab and triamcinolone. Subjects of the first period did not participate in the second period.

## Period 2

| | |
|---|---|
| Period 2 title | Ranibizumab vs Triamcinolone |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Carer |

Blinding implementation details:

There were two teams of study investigators: Investigators examining the patients were masked to treatment arm. Investigators applying the medication were masked to study results. Since Triamcinolone was injected no more than every three months sham injections were given intermittend to maintain patient masking.

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ranibizumab |

Arm description:

After a loading dose of three monthly injections of 0.5mg Lucentis, PRN treatment based on predefined morphological and functional retreatment criteria, that were reassessed monthly.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ranibizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled injector |
| Routes of administration | Intraocular use |

Dosage and administration details:

0.5 mg ranibizumab (Lucentis®, Novartis Pharma AG, Vienna, Austria) was injected at 3.5mm distance from the limbus through the inferotemporal pars plana.

| | |
|---|---|
| **Arm title** | Triamcinolone |

Arm description:

Patients with a clinical significant diabetic macular edema receive an intraocular injection of 8mg

triamcinolone at baseline under sterile conditions. 1 and 2 month after the baseline injection, patients receive a sham injection. After three month re-injection of 8mg Triamcinolone is performed as needed following a predefined protocol. In between two injection of 8mg Triamcinolone must be an temporal interval of at least 3 months.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Triamcinolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intraocular use |

Dosage and administration details:

Avolume of 0.1 ml containing 8mg triamcinolone (Volon A, Dermapharm GmbH) was injected at 3.5mm distance from the limbus through the inferotemporal pars plana.

| **Number of subjects in period 2** | Ranibizumab | Triamcinolone |
|---|---|---|
| Started | 15 | 15 |
| Completed | 10 | 15 |
| Not completed | 5 | 0 |
| Lost to follow-up | 5 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Bevacizumab |
| Reporting group description: | |
| After a loading dose of three monthly injections of 2.5mg Avastin, PRN treatment based on predefined morphological and functional retreatment criteria, that were reassessed monthly. | |
| Reporting group title | Triamcinolone |
| Reporting group description: | |
| 15 patients with a clinical significant diabetic macular edema receive an intraocular injection of 8mg triamcinolone at baseline under sterile conditions. 1 and 2 month after the baseline injection, patients receive a sham injection. After three month re-injection of 8mg Triamcinolone is performed as needed following a predefined protocol. In between two injection of 8mg Triamcinolone must be an temporal interval of at least 3 months. | |

| Reporting group values | Bevacizumab | Triamcinolone | Total |
|---|---|---|---|
| Number of subjects | 18 | 16 | 34 |
| 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) | 13 | 11 | 24 |
| From 65-84 years | 5 | 5 | 10 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62 | 60 | |
| standard deviation | ± 7.7 | ± 14.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 11 | 7 | 18 |
| Male | 7 | 9 | 16 |
| Best corrected visual acuity | | | |
| Best correcteed visual acuity (BCVA) was measured on a logarithmic scale ofthe minimum angle ofresolution (logMAR) using ETDRS charts at a distance of 2 m. | | | |
| Units: logMAR | | | |
| log mean | 0.3 | 0.32 | |
| inter-quartile range (Q1-Q3) | 0.19 to 0.416 | 0.197 to 0.432 | - |
| Central Retinal Subfield Thickness | | | |
| Central subfield retinal thickness (CSRT) was measured in the central mm using swept source OCT (optical coherence tomography) technology. | | | |
| Units: µm | | | |
| arithmetic mean | 505 | 490 | |
| inter-quartile range (Q1-Q3) | 438 to 572 | 433 to 546 | - |

## Subject analysis sets

| | |
|---|---|
| Subject analysis set title | Ranibizumab vs Triamcinolone |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Efficacy of the treatment with intravitreal administered injections of Ranibizumab (Lucentis®) ) compared with triamcinolone (Volon A®) in patients with diabetic macular edema

| **Reporting group values** | Ranibizumab vs Triamcinolone | | |
|---|---|---|---|
| Number of subjects | 25 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 64 | | |
| standard deviation | ± 13.6 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 7 | | |
| Male | 18 | | |
| Best corrected visual acuity | | | |
| Best correcteed visual acuity (BCVA) was measured on a logarithmic scale ofthe minimum angle ofresolution (logMAR) using ETDRS charts at a distance of 2 m. | | | |
| Units: logMAR<br>log mean<br>inter-quartile range (Q1-Q3) | | | |
| Central Retinal Subfield Thickness | | | |
| Central subfield retinal thickness (CSRT) was measured in the central mm using swept source OCT (optical coherence tomography) technology. | | | |
| Units: µm<br>arithmetic mean<br>inter-quartile range (Q1-Q3) | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Bevacizumab |

Reporting group description:

After a loading dose of three monthly injections of 2.5mg Avastin, PRN treatment based on predefined morphological and functional retreatment criteria, that were reassessed monthly.

| | |
|---|---|
| Reporting group title | Triamcinolone |

Reporting group description:

15 patients with a clinical significant diabetic macular edema receive an intraocular injection of 8mg triamcinolone at baseline under sterile conditions. 1 and 2 month after the baseline injection, patients receive a sham injection. After three month re-injection of 8mg Triamcinolone is performed as needed following a predefined protocol. In between two injection of 8mg Triamcinolone must be an temporal interval of at least 3 months.

| | |
|---|---|
| Reporting group title | Ranibizumab |

Reporting group description:

After a loading dose of three monthly injections of 0.5mg Lucentis, PRN treatment based on predefined morphological and functional retreatment criteria, that were reassessed monthly.

| | |
|---|---|
| Reporting group title | Triamcinolone |

Reporting group description:

Patients with a clinical significant diabetic macular edema receive an intraocular injection of 8mg triamcinolone at baseline under sterile conditions. 1 and 2 month after the baseline injection, patients receive a sham injection. After three month re-injection of 8mg Triamcinolone is performed as needed following a predefined protocol. In between two injection of 8mg Triamcinolone must be an temporal interval of at least 3 months.

| | |
|---|---|
| Subject analysis set title | Ranibizumab vs Triamcinolone |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Efficacy of the treatment with intravitreal administered injections of Ranibizumab (Lucentis®) ) compared with triamcinolone (Volon A®) in patients with diabetic macular edema

### Primary: Visual acuity after 12 months of treatment

| | |
|---|---|
| End point title | Visual acuity after 12 months of treatment |

End point description:

Best correcteed visual acuity (BCVA) was measured monthly on a logarithmic scale of the minimum angle ofresolution (logMAR) using ETDRS charts at a distance of 2 m.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

12 months

| End point values | Bevacizumab | Triamcinolone | Ranibizumab | Triamcinolone |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15[1] | 15[2] | 10[3] | 15[4] |
| Units: logMAR | | | | |
| log mean (inter-quartile range (Q1-Q3)) | 0.18 (0.064 to 0.303) | 0.36 (0.194 to 0.523) | 0.18 (0.123 to 0.286) | 0.36 (0.27 to 0.531) |

Notes:

[1] - Results from subjects, who finished the study.

[2] - Results from subjects, who finished the study.

[3] - Results from subjects, who finished the study.

[4] - Results from subjects, who finished the study.

## Statistical analyses

| **Statistical analysis title** | central retinal thickness analysis |
|---|---|
| Statistical analysis description: | |
| Repeated-measures-ANOVA will be used to reveal differences between macular edema measurements before and after treatment and between groups | |
| Comparison groups | Bevacizumab v Triamcinolone v Ranibizumab v Triamcinolone |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

## Primary: Central Retinal Subfield Thickness after 12 months

| End point title | Central Retinal Subfield Thickness after 12 months |
|---|---|
| End point description: | |
| Central subfield retinal thickness (CSRT) was measured in the central mm using swept source OCT (optical coherence tomography) technology. | |
| End point type | Primary |
| End point timeframe: | |
| 12 months. | |

| **End point values** | Bevacizumab | Triamcinolone | Ranibizumab | Triamcinolone |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 15 | 10 | 15 |
| Units: µm | | | | |
| number (not applicable) | 351 | 296 | 389 | 404 |

## Statistical analyses

| **Statistical analysis title** | central retinal thickness analysis |
|---|---|
| Comparison groups | Bevacizumab v Triamcinolone v Ranibizumab v Triamcinolone |

| | |
|---|---|
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: 12 months | |
| Adverse event reporting additional description: Intraocular pressure elevation >25mmHg | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 10.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Bevacizumab |
| Reporting group description: - | |
| Reporting group title | Triamcinolone |
| Reporting group description: - | |
| Reporting group title | Ranibizumab |
| Reporting group description: - | |

| Serious adverse events | Bevacizumab | Triamcinolone | Ranibizumab |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 30 (3.33%) | 0 / 10 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| myocardial infarction | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 30 (3.33%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Bevacizumab | Triamcinolone | Ranibizumab |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 7 / 30 (23.33%) | 1 / 10 (10.00%) |
| Eye disorders | | | |
| Elevated intraocular pressure | Additional description: IOP > 25mmHg | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 7 / 30 (23.33%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 7 | 1 |

## 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

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/24336297

http://www.ncbi.nlm.nih.gov/pubmed/29063703

http://www.ncbi.nlm.nih.gov/pubmed/29080915