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) 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 Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64		
standard deviation	± 13.6		
Gender categorical 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 log mean 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 arithmetic mean 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