



Clinical trial results:

Efficacy and safety of tocilizumab in patients with moderate to severe or sight-threatening TAO, who have poor response to treatment with pulse steroids. Phase III clinical trial, randomized, placebo-controlled, double-blind, parallel groups and multicenter study.

Summary

EudraCT number	2010-023841-31
Trial protocol	ES
Global end of trial date	27 October 2015

Results information

Result version number	v1 (current)
This version publication date	01 May 2019
First version publication date	01 May 2019
Summary attachment (see zip file)	Report for NCA (informe_resumen _resultados_GRC-TCL-2010-01-1.pdf) Article reference (article reference.pdf)

Trial information

Trial identification

Sponsor protocol code	GRC-TCL-2010-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01297699
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación Instituto de Investigación Sanitaria de Santiago de Compostela
Sponsor organisation address	Travesía da Choupana s/n, Santiago de Compostela, Spain,
Public contact	Fundación Instituto de Investigación Sanitaria de Santiago de Compostela, Fundación Instituto de Investigación Sanitaria de Santiago de Compostela, ma.teresa.cabaleiro.ocampo@sergas.es
Scientific contact	Fundación Instituto de Investigación Sanitaria de Santiago de Compostela, Fundación Instituto de Investigación Sanitaria de Santiago de Compostela, ma.teresa.cabaleiro.ocampo@sergas.es

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	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2015
Global end of trial reached?	Yes
Global end of trial date	27 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the efficacy of the administration of tocilizumab, in patients with OT of moderate to the threat of vision in active phase (according to the EUGOGO guidelines); With little or no response to glucocorticoid pulses.

- To observe the safety of the drug tocilizumab in these patients.

Protection of trial subjects:

Patients who during the visits of the study are detected laboratory values of liver function, neutrophil count and platelet count outside of normal parameters a dose adjustment should be made.

In case of a severe hypersensitivity reaction medication should be available for the treatment of hypersensitivity reactions for immediate use. These Medications include antihistamines, corticosteroids and adrenaline. If there is any sign or symptom of a possible reaction to the infusion, and the state cardiovascular remains stable: the infusion rate and the time of infusion should be lengthened; If the patient continues to show signs and symptoms of hypersensitivity, a dose of antihistamines should be administered via intramuscular or slow intravenous

In patients who experience severe reactions to the infusion with a collapse cardiovascular disease, the infusion should be interrupted and the patient should be treated as if it was an anaphylactic reaction with intravenous antihistamines, corticosteroids and adrenaline, if necessary. No more medication will be administered study and the patient will be definitively removed from it.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2013
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	Spain: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	30
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The ophthalmologist obtained the informed consent (IC) of each patient, to whom s/he explained the study design and procedures. The patients who fulfilled the eligibility criteria and selection criteria were enrolled onto the study. The patients' ID and the treatment number were assigned according to a list of pre-defined random codes.

Pre-assignment

Screening details:

All subjects were > 18 years of age, normal thyroid hormone levels and active GO, incomplete responders to corticosteroid pulses. The sight-threatening criteria were limited to patients with compressive optic neuropathy resolved by medical or surgical treatment who still required further anti-inflammatory treatment.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Pharmacists at the participant centers prepared tocilizumab in a sterile and pyrogen-free solution of 0.9% sodium chloride as well as a similar placebo solution, but the pharmacists were masked to the participants. Participants, people giving the interventions, those assessing outcomes, and those analyzing the data were masked to group assignment. There were no cases of unmasking throughout the entire masking process.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The placebo to be used is a pyrogen-free sterile solution of sodium chloride at 0.9% with a final volume of 100 mL, administered once every four weeks over the total sixteen-week period. The placebo will be prepared only insofar as necessary to mask its nature before its administration

Arm title	Intervention
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Arm description:

Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.

Arm type	Experimental
Investigational medicinal product name	TOCILIZUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The dosage of Tocilizumab is 8 mg/Kg of body weight, concentrate in solution for intravenous injection (each ml of concentrate contains 20 mg of Tocilizumab), and administered once every four weeks over a 16-week period. Once the Tocilizumab dosage has been adjusted for the patient's weight, the weight-appropriate volume of Tocilizumab is to substitute the same volume of solution in a 100 mL infusion bag, with the final volume always 100 mL. IMP should be administered at approximately the same time (four-hour margin), preferably in the morning and on the same day of the week (three-day margin).

Number of subjects in period 1	Control	Intervention
Started	17	15
Completed	17	15

Period 2

Period 2 title	Week 16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Pharmacists at the participant centers prepared tocilizumab in a sterile and pyrogen-free solution of 0.9% sodium chloride as well as a similar placebo solution, but the pharmacists were masked to the participants. Participants, people giving the interventions, those assessing outcomes, and those analyzing the data were masked to group assignment. There were no cases of unmasking throughout the entire masking process.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The placebo to be used is a pyrogen-free sterile solution of sodium chloride at 0.9% with a final volume of 100 mL, administered once every four weeks over the total sixteen-week period. The placebo will be prepared only insofar as necessary to mask its nature before its administration

Investigational medicinal product name	TOCILIZUMAB
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The dosage of Tocilizumab is 8 mg/Kg of body weight, concentrate in solution for intravenous injection (each ml of concentrate contains 20 mg of Tocilizumab), and administered once every four weeks over a 16-week period. Once the Tocilizumab dosage has been adjusted for the patient's weight, the weight-appropriate volume of Tocilizumab is to substitute the same volume of solution in a 100 mL infusion bag, with the final volume always 100 mL. IMP should be administered at approximately the same time (four-hour margin), preferably in the morning and on the same day of the week (three-day margin).

Arm title	Intervention
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Arm description:

Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.

Arm type	Experimental
Investigational medicinal product name	TOCILIZUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The dosage of Tocilizumab is 8 mg/Kg of body weight, concentrate in solution for intravenous injection (each ml of concentrate contains 20 mg of Tocilizumab), and administered once every four weeks over a 16-week period. Once the Tocilizumab dosage has been adjusted for the patient's weight, the weight-appropriate volume of Tocilizumab is to substitute the same volume of solution in a 100 mL infusion bag, with the final volume always 100 mL. IMP should be administered at approximately the same time (four-hour margin), preferably in the morning and on the same day of the week (three-day margin).

Number of subjects in period 2	Control	Intervention
Started	17	15
Completed	17	15

Period 3

Period 3 title	Week 40
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	Control
Arm description: The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: The placebo to be used is a pyrogen-free sterile solution of sodium chloride at 0.9% with a final volume of 100 mL, administered once every four weeks over the total sixteen-week period. The placebo will be prepared only insofar as necessary to mask its nature before its administration	
Arm title	Intervention

Arm description: Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.	
Arm type	Experimental
Investigational medicinal product name	TOCILIZUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
The dosage of Tocilizumab is 8 mg/Kg of body weight, concentrate in solution for intravenous injection (each ml of concentrate contains 20 mg of Tocilizumab), and administered once every four weeks over a 16-week period. Once the Tocilizumab dosage has been adjusted for the patient's weight, the weight-appropriate volume of Tocilizumab is to substitute the same volume of solution in a 100 mL infusion bag, with the final volume always 100 mL. IMP should be administered at approximately the same time (four-hour margin), preferably in the morning and on the same day of the week (three-day margin).

Number of subjects in period 3	Control	Intervention
Started	17	15
Completed	14	14
Not completed	3	1
Consent withdrawn by subject	1	-
Lost to follow-up	2	1

Baseline characteristics

Reporting groups

Reporting group title	Control
Reporting group description: The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.	
Reporting group title	Intervention
Reporting group description: Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.	

Reporting group values	Control	Intervention	Total
Number of subjects	17	15	32
Age categorical Units: Subjects			
Adults (18-64 years)	13	15	28
From 65-84 years	4	0	4
Age continuous Units: years			
median	47.5	45.07	
inter-quartile range (Q1-Q3)	41.1 to 57.4	38.9 to 50.5	-
Gender categorical Units: Subjects			
Female	13	11	24
Male	4	4	8
Anti-thyroid treatment Units: Subjects			
Yes	5	4	9
No	12	11	23
Replacement therapy Units: Subjects			
Yes	8	11	19
No	9	4	13
Prior thyroidectomy Units: Subjects			
Yes	3	2	5
No	14	13	27
Duration of GD			
GD=Graves Disease			
Units: Years			
median	1.45	2.24	
inter-quartile range (Q1-Q3)	0.35 to 3.9	0.69 to 10.3	-
Duration of GO			
GO=Graves orbitopathy			
Units: Years			
median	1.07	1.09	
inter-quartile range (Q1-Q3)	0.49 to 2.9	0.69 to 4.0	-
GOQoL function			

GOQoL=Graves orbitopathy quality of life			
Units: Points			
median	25.0	72.2	
inter-quartile range (Q1-Q3)	16.7 to 44.0	38.9 to 83.3	-
GOQoL Appearence			
GOQoL=Graves orbitopathy quality of life			
Units: points			
median	45.0	50.0	
inter-quartile range (Q1-Q3)	30.0 to 65.0	45.0 to 55.0	-
SF-36 - Mental function			
SF-36=standard SF36 questionnaire (short form 36)			
Units: unit(s)			
median	62.4	69.1	
inter-quartile range (Q1-Q3)	33.1 to 80.5	44.6 to 82.5	-
SF-36 - Physical function			
SF-36=standard SF36 questionnaire (short form 36)			
Units: unit(s)			
median	50.0	71.0	
inter-quartile range (Q1-Q3)	34.0 to 72.0	50.0 to 78.0	-
ESR			
ESR=Erythrocyte sedimentation rate			
Units: mm/h			
median	16.0	12.0	
inter-quartile range (Q1-Q3)	10.0 to 24.0	7.0 to 21.0	-
CRP			
CRP=C-reactive protein			
Units: mg/dL			
median	0.70	0.42	
inter-quartile range (Q1-Q3)	0.26 to 1.60	0.10 to 1.0	-
TSH			
TSH=Thyroid-stimulating hormone			
Units: mIU/L			
median	0.80	0.15	
inter-quartile range (Q1-Q3)	0.50 to 2.8	0.02 to 2.8	-
TSI			
TSI=Thyroid-stimulating immunoglobulin			
Units: IU/L			
median	7.5	24.4	
inter-quartile range (Q1-Q3)	1.1 to 31.3	8.2 to 35.5	-
Anti-TPO			
Anti-TPO=anti-thyroid peroxidase antibodies			
Units: IU/mL			
median	36.5	41.2	
inter-quartile range (Q1-Q3)	18.41 to 183	28.0 to 200.0	-
Anti-TG			
Anti-TG=antithyroglobulin antibodies			
Units: IU/mL			
median	20.0	21.5	
inter-quartile range (Q1-Q3)	8.3 to 100	15.0 to 456.8	-
Hemoglobin			
Units: g/dL			
median	12.6	14.3	

inter-quartile range (Q1-Q3)	12.6 to 14.1	13.1 to 15.2	-
Hematocrit			
Units: percent			
median	37.7	42.7	
inter-quartile range (Q1-Q3)	36.1 to 41.6	39.1 to 43.5	-
Leukocytes			
Units: cells/microlitre			
median	6.4	4.67	
inter-quartile range (Q1-Q3)	4.76 to 7.56	3.84 to 5.74	-
Platelets			
Units: cells/microlitre			
median	252	185	
inter-quartile range (Q1-Q3)	212 to 309	164 to 219	-
Aspartate aminotransferase			
Units: U/L			
median	18	23.5	
inter-quartile range (Q1-Q3)	15 to 22	19 to 23.5	-
Alanine aminotransferase			
Units: U/L			
median	13	29	
inter-quartile range (Q1-Q3)	9 to 20	18 to 37	-
Alkaline phosphatase			
Units: U/L			
median	94	113.5	
inter-quartile range (Q1-Q3)	62 to 120	68 to 123.5	-
Bilirubin			
Units: mg/dL			
median	0.6	0.64	
inter-quartile range (Q1-Q3)	0.48 to 0.78	0.56 to 0.88	-
Cholesterol			
Units: mg/dL			
median	194	201	
inter-quartile range (Q1-Q3)	164 to 214	186 to 252	-
Triglycerides			
Units: mg/dL			
median	80	116	
inter-quartile range (Q1-Q3)	70 to 113	56 to 148	-
HDL			
Units: mg/dL			
median	50	64	
inter-quartile range (Q1-Q3)	38.7 to 53	52 to 82	-
LDL			
Units: mg/dL			
median	122	124	
inter-quartile range (Q1-Q3)	85 to 153.51	104 to 154	-

End points

End points reporting groups

Reporting group title	Control
Reporting group description: The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.	
Reporting group title	Intervention
Reporting group description: Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.	
Reporting group title	Control
Reporting group description: The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.	
Reporting group title	Intervention
Reporting group description: Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.	
Reporting group title	Control
Reporting group description: The intravenous administration (via a parenteral solution) of a sterile, pyrogen-free solution of 0.9% sodium chloride every four weeks during a total of sixteen weeks.	
Reporting group title	Intervention
Reporting group description: Intravenous administration (via a parenteral solution) of a single 8 mg/Kg dose of Tocilizumab every four weeks during a total of sixteen weeks.	

Primary: CAS improvement

End point title	CAS improvement
End point description: The efficacy of the administration of the medicine Tocilizumab will be measured as an improvement in the disorder, stated as a reduction in the CAS (clinical activity score) of 2 or more points on a scale of 10. This will be measured on every visit and compared before treatment (week - 4/0), with after treatment (week 16) and after completion of the follow-up period (week 40). Exploratory analyses of other variables of secondary outcomes may be undertaken. The activity of the disease will be measured using a clinical activity score (CAS). CAS is based on well-known classic clinical signs, such as pain, reddening, oedema and ocular dysfunction. CAS consists of 10 items and a point is assigned for each item, all of them are of equal importance and the final score is obtained by adding up all the points for the 10 items. The final score will be between 0 and 10. A clinical activity score of ≥ 4 indicates that the GO is in the active phase.	
End point type	Primary
End point timeframe: Proportion of patients with improvements in CAS by at least 2 at week 16 and at week 40.	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
number (confidence interval 95%)	58.8 (36 to 78.3)	93.3 (70.1 to 98.8)	58.9 (36.0 to 78.3)	86.7 (62.1 to 96.2)

Statistical analyses

Statistical analysis title	STATISTICAL ANALYSIS
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Statistical analysis description:

The ITT population included all randomized patients who received at least 1 infusion of the study treatment. Fisher test analyzed categorical variables, and nonparametric tests compared changes from baseline in levels of anti-TPO, anti-TG, TSH, TSI, SF-36, and GOQoL. OR estimation was used to measure the effect size. Last observation was carried forward when a data point was missing. Patients discontinuing the study were imputed as nonresponders. A 2-sided $< .05$ was considered the limit of significance

Comparison groups	Control v Intervention
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact

Secondary: Anti-Tg levels, median improvement

End point title	Anti-Tg levels, median improvement
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End point description:

End point type	Secondary
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End point timeframe:

Week 16

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: IU/mL				
median (inter-quartile range (Q1-Q3))	0.0 (-3.2 to 0.0)	-5.1 (-29.8 to 0.00)	0.0 (-14.2 to 0.0)	-2.5 (-4.7 to 0.0)

Statistical analyses

No statistical analyses for this end point

Secondary: PtGA median improvement

End point title	PtGA median improvement
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End point description:

End point type	Secondary
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End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
median (inter-quartile range (Q1-Q3))	-0.0 (-1.9 to 0.2)	-1.2 (-2.5 to 0.0)	-0.0 (-2.2 to 0.0)	0.1 (0.0 to 15.3)

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36, median improvement

End point title	SF-36, median improvement
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End point description:

End point type	Secondary
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End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
median (inter-quartile range (Q1-Q3))	0.0 (-8.0 to 2.2)	2.3 (-4.7 to 16.2)	0.0 (-6.7 to 1.0)	0.1 (0.0 to 15.3)

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36, mental function

End point title	SF-36, mental function
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End point description:

End point type	Secondary
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End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
median (inter-quartile range (Q1-Q3))	-2.2 (-29.2 to 8.7)	7.5 (-9.3 to 21.6)	-9.3 (-27.3 to 3.6)	9.6 (-8.1 to 32.9)

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36, physical function

End point title	SF-36, physical function
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End point description:

End point type	Secondary
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End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
median (inter-quartile range (Q1-Q3))	-3.0 (-23.5 to 4.0)	2.0 (-2.5 to 16.5)	-10.5 (-34.0 to 12.5)	3.0 (-19.0 to 19.5)

Statistical analyses

No statistical analyses for this end point

Secondary: GOQoL, % patients (CI) with ≥ 8 improvement - Functioning

End point title	GOQoL, % patients (CI) with ≥ 8 improvement - Functioning
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End point description:

End point type	Secondary
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End point timeframe:
Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
number (confidence interval 95%)	35.2 (17.3 to 58.7)	46.7 (24.8 to 69.9)	35 (17.3 to 58.7)	46.7 (24.8 to 69.9)

Statistical analyses

No statistical analyses for this end point

Secondary: GOQoL, % patients (CI) with ≥ 8 improvement - Appearance

End point title GOQoL, % patients (CI) with ≥ 8 improvement - Appearance

End point description:

End point type Secondary

End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
number (confidence interval 95%)	17.6 (6.1 to 41.0)	40.0 (19.9 to 64.2)	29.4 (13.2 to 53.1)	33.3 (15.1 to 58.2)

Statistical analyses

No statistical analyses for this end point

Secondary: EUGOGO composite score improvement, % of patients

End point title EUGOGO composite score improvement, % of patients

End point description:

End point type Secondary

End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
number (confidence interval 95%)	29.4 (13.3 to 53.1)	73.3 (48.0 to 89.1)	17.6 (6.2 to 41.0)	66.7 (41.7 to 84.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Exophtalmos -Hertel-

End point title	Exophtalmos -Hertel-
End point description:	
End point type	Secondary
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: mm				
median (inter-quartile range (Q1-Q3))	23.0 (19.5 to 24)	20.5 (18 to 22)	23.2 (19 to 24)	20.7 (18.5 to 22)

Statistical analyses

No statistical analyses for this end point

Secondary: Δ Exophtalmos from week 0

End point title	Δ Exophtalmos from week 0
End point description:	
End point type	Secondary
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: mm				
median (inter-quartile range (Q1-Q3))	0.0 (-1.0 to 0.5)	-1.5 (-2.0 to 0.5)	0.0 (-0.5 to 1.0)	-1.5 (-2.0 to 0.5)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Retro-ocular pain

End point title	Retro-ocular pain
End point description: Percentage (confidence interval) of Patients With No Worsening in the Components of the Clinical Activity Score	
End point type	Post-hoc
End point timeframe: Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
number (confidence interval 95%)	64.7 (41.3 to 82.7)	86.7 (62.1 to 96.2)	64.7 (41.3 to 82.7)	80.0 (54.8 to 92.9)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Pain extreme positions

End point title	Pain extreme positions
End point description:	
End point type	Post-hoc
End point timeframe: Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
number (confidence interval 95%)	52.9 (30.9 to 73.8)	60.0 (35.7 to 80.1)	52.9 (30.9 to 73.8)	80.0 (54.8 to 92.9)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Eyelid erythema

End point title	Eyelid erythema
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	70.5 (46.9 to 86.7)	93.3 (70.1 to 98.8)	64.7 (41.3 to 82.7)	86.6 (62.1 to 96.2)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Hyperemia

End point title	Hyperemia
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	41.1 (21.6 to 64)	80 (64.8 to 92.9)	64.7 (41.3 to 82.7)	80 (54.8 to 92.9)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Edema

End point title	Edema
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	29.4 (13.2 to 53.1)	53.3 (30.1 to 75.1)	41.1 (21.6 to 64)	60 (35.7 to 80.1)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Chemosis

End point title	Chemosis
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	35.3 (17.3 to 58.7)	80 (54.8 to 92.9)	47 (26.1 to 69)	60 (35.7 to 80.1)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Caruncular swelling

End point title	Caruncular swelling
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	64.7 (41.3 to 82.7)	86.6 (62.1 to 96.2)	53.3 (30.1 to 75.1)	80 (54.8 to 92.9)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Exophtalmos

End point title	Exophtalmos
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	82.3 (60 to 94)	93.3 (70.1 to 98.8)	82.3 (60 to 94)	86.6 (62.1 to 96.2)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Motility

End point title	Motility
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	64.7 (41.3 to 82.7)	93.3 (70.1 to 98.8)	76.4 (52.7 to 90.4)	86.6 (62.1 to 96.2)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Visual acuity

End point title	Visual acuity
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: percent				
median (inter-quartile range (Q1-Q3))	76.4 (52.7 to 90.4)	93.3 (70.1 to 98.8)	70.6 (46.9 to 86.7)	93.3 (70.1 to 98.8)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Improvement in eyelid aperture by at least 3 mm

End point title	Improvement in eyelid aperture by at least 3 mm
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
number (not applicable)	2	2	7	5

Statistical analyses

No statistical analyses for this end point

Post-hoc: Improvement in signs of soft tissue involvement by at least 2 grades

End point title	Improvement in signs of soft tissue involvement by at least 2 grades
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
number (not applicable)	10	12	14	13

Statistical analyses

No statistical analyses for this end point

Post-hoc: Improvement in Bahn/Gorman diplopia score or at least 8 grades

End point title	Improvement in Bahn/Gorman diplopia score or at least 8 grades
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
number (not applicable)	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Improvement in proptosis by at least 2 mm

End point title	Improvement in proptosis by at least 2 mm
End point description:	
End point type	Post-hoc
End point timeframe:	
Week 16 and week 40	

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
number (not applicable)	8	4	14	6

Statistical analyses

No statistical analyses for this end point

Post-hoc: Improvement in CAS by at least 2 points

End point title	Improvement in CAS by at least 2 points
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End point description:

End point type	Post-hoc
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End point timeframe:

Week 16 and week 40

End point values	Control	Intervention	Control	Intervention
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	15
Units: unit(s)				
number (not applicable)	10	10	14	13

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

OAA / pregnancies were collected as soon as the patient signs the Informed Consent until 30 days after the patient's last visit. Study Information about AAs that have been produced between the previous visit and the current visit were requested.

Assessment type	Systematic
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Dictionary used

Dictionary name	CPMP/ICH/135/95
Dictionary version	2002

Reporting groups

Reporting group title	Control - week 16
Reporting group description: -	
Reporting group title	Intervention - week 16
Reporting group description: -	
Reporting group title	Control - week 40
Reporting group description: -	
Reporting group title	Intervention - week 40
Reporting group description: -	

Serious adverse events	Control - week 16	Intervention - week 16	Control - week 40
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Transaminases increased	Additional description: Resolved. Not related to treatment.		
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 17 (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
Renal and urinary disorders			
Pyelonephritis acute	Additional description: Resolved. Not related to treatment.		
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Intervention - week 40		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Hepatobiliary disorders			
Transaminases increased	Additional description: Resolved. Not related to treatment.		
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Pyelonephritis acute	Additional description: Resolved. Not related to treatment.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Control - week 16	Intervention - week 16	Control - week 40
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	9 / 15 (60.00%)	7 / 17 (41.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 17 (5.88%)	3 / 15 (20.00%)	1 / 17 (5.88%)
occurrences (all)	2	9	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 17 (17.65%)	0 / 15 (0.00%)	3 / 17 (17.65%)
occurrences (all)	3	0	3
Neutropenia	Additional description: Grade I		
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia	Additional description: Grade I		
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Ocular symptoms (pain)			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Gastrointestinal disorders			

Infection - gastroenteritis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	2 / 15 (13.33%) 2	1 / 17 (5.88%) 1
Respiratory, thoracic and mediastinal disorders Infection - respiratory tract subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	5 / 15 (33.33%) 6	1 / 17 (5.88%) 1
Renal and urinary disorders Infection - urinary tract subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 15 (6.67%) 2	0 / 17 (0.00%) 0
Metabolism and nutrition disorders Hypercholesterolemia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 15 (13.33%) 2	1 / 17 (5.88%) 1

Non-serious adverse events	Intervention - week 40		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 15 (80.00%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 11		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	Additional description: Grade I 1 / 15 (6.67%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	Additional description: Grade I 1 / 15 (6.67%) 1		
Eye disorders Ocular symptoms (pain) subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Gastrointestinal disorders			

Infection - gastroenteritis subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Respiratory, thoracic and mediastinal disorders Infection - respiratory tract subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Renal and urinary disorders Infection - urinary tract subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Metabolism and nutrition disorders Hypercholesterolemia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2011	Protocol version 2
10 May 2012	Protocol version 3
13 December 2012	Protocol version 4

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/30081019>