Clinical trial results:
Assessment of Anatomical and Functional Outcomes in Patients Treated with Ocriplasmin for Vitreomacular Traction/Symptomatic Vitreomacular Adhesion
(VMT/sVMA)

Summary

EudraCT number	2013-005464-25
Trial protocol	HU GB DE IT ES NL PT BE PL FR
Global end of trial date	02 September 2015
Results information	
Result version number	v1 (current)
This version publication date	30 August 2016
First version publication date	30 August 2016

Trial information

Trial identification	
Sponsor protocol code	M-13-056
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02035748
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Alcon, A Novartis Division
Sponsor organisation address	6201 S. Freeway, Fort Worth, Texas, United States, 76134
Public contact	EMEA Medical Affairs Lead, Pharma, Alcon, A Novartis Division, +1 888-451-3937, alcon.medinfo@alcon.com
Scientific contact	EMEA Medical Affairs Lead, Pharma, Alcon, A Novartis Division, +1 888-451-3937, alcon.medinfo@alcon.com

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	02 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to observe the anatomical and functional outcomes of ocriplasmin (JETREA®) over a 6-month follow-up period. After receiving a single intravitreal injection as per country's product label (Day 0), subjects were followed for a 6-month period (Day 180).

Protection of trial subjects:

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 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	Netherlands: 35
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 60
Country: Number of subjects enrolled	Belgium: 40
Country: Number of subjects enrolled	France: 99
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Canada: 67
Worldwide total number of subjects	468
EEA total number of subjects	401

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	81
From 65 to 84 years	364
85 years and over	23

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 87 study centers located in Europe and Canada (10 Italy, 5 Netherlands, 4 Poland, 4 Portugal, 12 Spain, 15 United Kingdom, 3 Belgium, 12 France, 9 Germany, 5 Hungary, and 8 Canada).

Pre-assignment

Screening details:

Of the 628 enrolled, 160 subjects were exited prior to initiation of treatment. This reporting group includes all treated subjects (468).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ocriplasmin

Arm description:

Ocriplasmin 0.125 mg in a 0.1 mL volume administered as a single dose by intravitreal injection

Arm type	Experimental
Investigational medicinal product name	Ocriplasmin
Investigational medicinal product code	
Other name	JETREA
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

0.5 mg/0.2 mL solution for injection

Number of subjects in period 1	Ocriplasmin
Started	468
Full Analysis Set	466
Completed	448
Not completed	20
Physician decision	3
Adverse event, non-fatal	5
Death	3
Progressive disease	1
Lost to follow-up	2
Withdrawal by subject	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Ocriplasmin 0.125 mg in a 0.1 mL volume administered as a single dose by intravitreal injection	

Reporting group values	Overall study	Total	
Number of subjects	468	468	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	71.7		
standard deviation	± 8.3	-	
Gender categorical Units: Subjects			
Female	345	345	
Male	123	123	

End points

End points reporting groups

Reporting group title	Ocriplasmin
Reporting group description:	
Ocriplasmin 0.125 mg in a 0.1 mL volume administered as a single dose by intravitreal injection	

Primary: Proportion of Subjects With Nonsurgical Resolution of Focal Vitreomacular Traction (VMT/VMA) at Day 28, as Determined by Central Reading Center (CRC) Spectral Domain Optical Coherence Tomography (SD-OCT) Evaluation

End point title	Proportion of Subjects With Nonsurgical Resolution of Focal Vitreomacular Traction (VMT/VMA) at Day 28, as Determined by Central Reading Center (CRC) Spectral Domain Optical Coherence Tomography (SD-OCT) Evaluation[1]

End point description:

Vitreous separation was assessed by SD-OCT using scores ranging from 1 (vitreous attached from macula to ON; separated elsewhere cannot determine foveal) to 12 (unable to determine state of separation). Nonsurgical resolution was defined as a change from baseline score of 5/6/8 to 7/9/10 at Day 28. The assessment of resolution of VMT/sVMA was based upon the anatomical resolution of VMA only, i.e. no resolution of the related symptoms was considered. Thus, the term VMA is used interchangeably with VMT/sVMA. Proportion of subjects is presented as a percentage, with percentage based on the number of subjects who have VMT/sVMA at baseline and SD-OCT value at Day 28. One eye (study eye) contributed to the analysis.

Subjects treated with IP with at least one post-treatment SD-OCT measurement (FAS). Missing data imputed using the last observation carried forward (LOCF) method. Subjects with vitrectomy after VMT/sVMA resolution were considered 'no resolution' after timepoint of vitrectomy.

End point type	Primary

End point timeframe:

Baseline, Day 28

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed

End point values	Ocriplasmin			
Subject group type	Reporting group			
Number of subjects analysed	466			
Units: percentage of subjects				
number (not applicable)	47.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Nonsurgical Change From Baseline in Best-corrected Visual Acuity (BCVA) at Distance

End point title	Nonsurgical Change From Baseline in Best-corrected Visual Acuity (BCVA) at Distance

End point description:

BCVA (with spectacles or other visual corrective devices) was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) testing at 4 meters. The charts contain 14 rows of letters. BCVA was calculated as the number of letters read correctly and improvement defined as an increase (gain) in letters read from the baseline assessment. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data imputed using LOCF. BCVA values after a vitrectomy were imputed with the last non-missing value prior to the vitrectomy.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Day 28, Day 90, Day 180

End point values	Ocriplasmin			
Subject group type	Reporting group			
Number of subjects analysed	448			
Units: letters				
arithmetic mean (standard deviation)				
Change from baseline at Day 28	1.7 (± 6.7)			
Change from baseline at Day 90	3 (± 7.07)			
Change from baseline at Day 180	3.5 (± 7.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Nonsurgical Closure of Macular Hole (MH), if Present at Baseline

End point title	Proportion of Subjects With Nonsurgical Closure of Macular Hole (MH), if Present at Baseline

End point description:

The closure of macular hole (a full thickness defect of the retinal tissure involving the anatomical fovea) is defined as a flattened and reattached hole rim along the whole circumference of macular hole. Closure was determined by SD-OCT evaluation and the percentage of subjects tabulated. Proportion of subjects is presented as a percentage, with percentage based on the number of subjects who had macular hole at baseline and OCT value at each specific visit. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data imputed using LOCF. Subjects who had vitrectomy after MH closure were considered as 'no MH closure' after the timepoint of vitrectomy.

End point type	Secondary

End point timeframe:

Day 28, Day 90, Day 180

End point values	Ocriplasmin			
Subject group type	Reporting group			
Number of subjects analysed	86			
Units: percentage of subjects				
number (not applicable)				
Day 28	39.5			
Day 90	40.7			
Day 180	41.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Nonsurgical Resolution of VMT/sVMA

End point title	Proportion of Subjects With Nonsurgical Resolution of VMT/sVMA

End point description:

Vitreous separation was assessed by SD-OCT using scores ranging from 1 (vitreous attached from macula to ON; separated elsewhere cannot determine foveal) to 12 (unable to determine state of separation). Nonsurgical resolution was defined as a change from baseline score of 5/6/8 to 7/9/10 at Day 90 and Day 180. The assessment of resolution of VMT/sVMA was based upon the anatomical resolution of VMA only, i.e. no resolution of the related symptoms was considered. Thus, the term VMA is used interchangeably with VMT/sVMA. Proportion of subjects is presented as a percentage, with percentage based on the number of subjects who have VMT/sVMA at baseline and SD-OCT value at Day 90/Day 180. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data imputed using LOCF. Subjects who had vitrectomy after VMT/sVMA resolution were considered as 'no resolution' after the timepoint of vitrectomy.

End point type	Secondary

End point timeframe:

Baseline, Day 90, Day 180

End point values	Ocriplasmin			
Subject group type	Reporting group			
Number of subjects analysed	466			
Units: percentage of subjects				
number (not applicable)				
Day 90	47.9			
Day 180	49.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Experiencing Pars Plana Vitrectomy (PPV) at Day 180

End point title	Proportion of Subjects Experiencing Pars Plana Vitrectomy (PPV) at Day 180

End point description:

Pars plana vitrectomy (the surgical removal of vitreous gel from the eye) was captured in Concomitant Ocular Procedures. Proportion of subjects is reported as a percentage. One eye (study eye) contributed to the analysis.

Full Analysis Set

End point type	Secondary

End point timeframe:

Day 180

End point values	Ocriplasmin			
Subject group type	Reporting group			
Number of subjects analysed	466			
Units: percentage of subjects				
number (not applicable)	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Nonsurgical Change From Baseline in Central Foveal Thickness (CFT)

End point title	Mean Nonsurgical Change From Baseline in Central Foveal Thickness (CFT)

End point description:

Nonsurgical change in central foveal thickness (CFT values after a vitrectomy were imputed with the last non-missing value prior to the vitrectomy) was determined by subtracting the measurements in subretinal fluid and retinal pigment epithelium (RPE) elevations and/or SHRM (subretinal hyper-reflective material such as choroidal neovascularization (CNV)) from the value in total retinal measurement. A lower CFT indicates improvement. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data is imputed using LOCF. CFT values after a vitrectomy were imputed with the last non-missing value prior to the vitrectomy.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Day 28, Day 180

End point values	Ocriplasmin			
Subject group type	Reporting group			
Number of subjects analysed	466			
Units: micrometers				
arithmetic mean (standard deviation)				
Baseline (Day 0), n=466	276.1 (± 166.4)			

Change from baseline at Day 28, n=465 Change from baseline at Day 180, n=466	-43.2 (± 113.47) -45.4 (± 131.84)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected for the duration of a subject's participation in the study (up to 7 months). Ocular AEs are presented for both study eye and non-study eye combined. AEs are reported as treatment-emergent.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a subject regardless of the causal relationship to the study medication. AEs could be volunteered or solicited by the Investigator or study personnel.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Ocriplasmin

Reporting group description:

All subjects exposed to the investigational product

Serious adverse events	Ocriplasmin		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 468 (9.83%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Investigations			
Colonoscopy			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer metastatic			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oesophageal carcinoma			

subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial carcinoma				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Surgical and medical procedures			
Cardioversion			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear operation			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Heart valve replacement			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip arthroplasty			
subjects affected / exposed	2 / 468 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip surgery			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lithotripsy			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal stone removal			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shoulder operation			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitrectomy			

subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disturbance in attention			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ciliary zonular dehiscence			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Macular hole			
subjects affected / exposed	8 / 468 (1.71%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	4 / 468 (0.85%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		

Visual acuity reduced				
subjects affected / exposed	5 / 468 (1.07%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Vitreous adhesions				
subjects affected / exposed	2 / 468 (0.43%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 468 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Rectal prolapse				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pickwickian syndrome				
subjects affected / exposed	1 / 468 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 468 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Ocriplasmin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 468 (52.78%)		
Eye disorders			
Colour blindness acquired			
subjects affected / exposed	26 / 468 (5.56%)		
occurrences (all)	26		
Eye pain			
subjects affected / exposed	40 / 468 (8.55%)		
occurrences (all)	41		
Macular oedema			

subjects affected / exposed	52 / 468 (11.11%)		
occurrences (all)	53		
Photophobia			
subjects affected / exposed	24 / 468 (5.13%)		
occurrences (all)	27		
Photopsia			
subjects affected / exposed	104 / 468 (22.22%)		
occurrences (all)	114		
Vision blurred			
subjects affected / exposed	54 / 468 (11.54%)		
occurrences (all)	62		
Visual acuity reduced			
subjects affected / exposed	127 / 468 (27.14%)		
occurrences (all)	138		
Vitreous floaters			
subjects affected / exposed	78 / 468 (16.67%)		
occurrences (all)	93		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2014	The purpose of this amendment was to include additional exclusion criteria to ensure that patients for whom treatment was not recommended were not enrolled in this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported