Clinical trial results:
A Multicenter, Double-masked, Randomized Study to Compare the Safety and Efficacy of an Investigational Eye Drop Formulation with OPTIVE™ Unit-Dose for 3 Months in Subjects with Dry Eye Disease

Summary

EudraCT number	2012-002238-35
Trial protocol	GB BE DE IT ES
Global end of trial date	23 May 2014

Results information

Result version number	v1 (current)
This version publication date	30 March 2016
First version publication date	30 March 2016

Trial information

Trial identification

Sponsor protocol code	11002X-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01664949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow, United Kingdom,
Public contact	Allergan Limited EU Regulatory Dept, Allergan Limited, +44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	Allergan Limited EU Regulatory Dept, Allergan Limited, +44 1628 494444, ml-eu_reg_affairs@allergan.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	08 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2014
Global end of trial reached?	Yes
Global end of trial date	23 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the safety and efficacy of a carboxymethylcellulose based eye drop formulation compared with carboxymethylcellulose based preservative-free lubricant eye drops [OPTIVE Unit-dose (UD)] in subjects with dry eye disease.

Protection of trial subjects:

All participants were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 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	Australia: 112
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Spain: 82
Country: Number of subjects enrolled	United Kingdom: 30
Worldwide total number of subjects	460
EEA total number of subjects	318

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)	297
From 65 to 84 years	159
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with signs and symptoms of dry eye disease were enrolled in one of 2 treatment groups: Carboxymethylcellulose Based Eye Drop Formulation A or OPTIVE Unit-dose (UD).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Carboxymethylcellulose Based Eye Drop Formulation A

Arm description:

Carboxymethylcellulose Based Eye Drop Formulation A 1-2 drops in each eye as needed at least 2 times daily for 90 days.

Arm type	Experimental
Investigational medicinal product name	Carboxymethylcellulose Based Eye Drop Formulation A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Ocular use

Dosage and administration details:

1 to 2 drops in each eye as needed, at least twice daily

Arm title	OPTIVE UD

Arm description:

Carboxymethylcellulose Based Preservative-Free Lubricant Eye Drops (OPTIVE UD) 1-2 drops in each eye as needed at least 2 times daily for 90 days.

Arm type	Active comparator
Investigational medicinal product name	OPTIVE UD
Investigational medicinal product code	
Other name	OPTAVA™, OPTIVE™
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Ocular use

Dosage and administration details:

1 to 2 drops in each eye as needed, at least twice daily

Number of subjects in period 1	Carboxymethylcellulose Based Eye Drop Formulation A	OPTIVE UD
Started	224	236
Completed	200	211
Not completed	24	25
Adverse event, non-fatal	11	12
Personal Reasons	3	4
Lost to follow-up	1	2
Other Miscellaneous Reasons	3	1
Lack of efficacy	1	1
Protocol deviation	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Carboxymethylcellulose Based Eye Drop Formulation A
Reporting group description:	
Carboxymethylcellulose Based Eye Drop Formulation A 1-2 drops in each eye as needed at least 2 times daily for 90 days.	
Reporting group title	OPTIVE UD
Reporting group description:	
Carboxymethylcellulose Based Preservative-Free Lubricant Eye Drops (OPTIVE UD) 1-2 drops in each eye as needed at least 2 times daily for 90 days.	

Reporting group values	Carboxymethylcellulose Based Eye Drop Formulation A	OPTIVE UD	Total
Number of subjects	224	236	460
Age categorical Units: Subjects			
< 30 years	9	10	19
30 to 40 years	15	15	30
> 40 years	200	211	411
Age continuous Units: years			
arithmetic mean	59.6	57.6	
standard deviation	± 13.77	± 13.65	-
Gender, Male/Female Units: Participants			
Female	182	189	371
Male	42	47	89

End points

End points reporting groups

Reporting group title	Carboxymethylcellulose Based Eye Drop Formulation A
Reporting group description:	
Carboxymethylcellulose Based Eye Drop Formulation A 1-2 drops in each eye as needed at least 2 times daily for 90 days.	
Reporting group title	OPTIVE UD
Reporting group description:	
Carboxymethylcellulose Based Preservative-Free Lubricant Eye Drops (OPTIVE UD) 1-2 drops in each eye as needed at least 2 times daily for 90 days.	

Primary: Change from Baseline in Ocular Surface Disease Index (OSDI) Score at Day 90

End point title	Change from Baseline in Ocular Surface Disease Index (OSDI) Score at Day 90[1]
End point description:	
The OSDI consists of 12 questions to assess visual function, ocular symptoms and environmental triggers related to dry eye. Each of the 12 questions is assessed using a 5-point scale (0=none of the time; 4 = all of the time) which is converted to a total score between 0-100. OSDI total scores of 0-12=normal (best), 13-22= mild ocular surface disease, 23-32 =moderate ocular surface disease, and 33-100=severe ocular surface disease (worst). A negative number change from Baseline indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline, Day 90	

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 is reported for this outcome measure

End point values	Carboxymethylcellulose Based Eye Drop Formulation A	OPTIVE UD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	198		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=196,198)	41.77 (± 14.018)	40.92 (± 13.31)		
Change from Baseline at Day 90 (n=181,185)	-16.88 (± 17.496)	-15.97 (± 16.146)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tear Break-up Time (TBUT)

End point title	Change from Baseline in Tear Break-up Time (TBUT)

End point description:

TBUT is the time in seconds for the tear film to visually break up after a complete blink. The average of 3 consecutive observations is reported for each participant. The longer it takes, the more stable the tear film. The eye with the shorter average TBUT at Baseline was used for analysis. A positive number change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Day 90

End point values	Carboxymethyl cellulose Based Eye Drop Formulation A	OPTIVE UD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	198		
Units: seconds				
arithmetic mean (standard deviation)				
Baseline (n=196,198)	4.5 (± 1.868)	4.44 (± 1.894)		
Change from Baseline at Day 90 (n=181,185)	2.69 (± 5.167)	2.24 (± 3.262)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Corneal Staining

End point title	Change from Baseline in Corneal Staining

End point description:

Staining of the cornea following ocular administration of fluorescein dye was graded using a 6-point scale (0=no staining, 5=diffuse staining). The eye with the higher score at Baseline was used for analysis. The higher the grade score, the worse the dry eye severity. A negative number change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Day 90

End point values	Carboxymethyl cellulose Based Eye Drop Formulation A	OPTIVE UD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	198		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=196,198)	1.5 (± 0.99)	1.6 (± 0.99)		
Change from Baseline at Day 90 (n=182, 184)	-0.7 (± 0.88)	-0.9 (± 0.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Conjunctival Staining

End point title	Change from Baseline in Conjunctival Staining

End point description:

Staining of the conjunctiva following ocular administration of lissamine green dye was graded using a 6-point scale (0=no staining, 5=diffuse staining). Conjunctival staining has 2 zones, nasal and temporal, which are added together to provide the total staining score. The eye with the higher score at Baseline was used for analysis. The higher the grade score, the worse the dry eye severity. A negative number change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Day 90

End point values	Carboxymethyl cellulose Based Eye Drop Formulation A	OPTIVE UD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	198		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=196,198)	2.8 (± 1.7)	3 (± 1.79)		
Change from Baseline at Day 90 (n= 181, 185)	-1.3 (± 1.57)	-1.4 (± 1.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Schirmer Test

End point title	Change from Baseline in the Schirmer Test

End point description:

The Schirmer's Test measures the rate of the secretion of tears produced by the eye over 5 minutes. The results indicate the presence of dry eye. The eye with the lower value at Baseline was used for Analysis. Normal = greater than or equal to 15 millimeters (mm) of tears, Dry Eye = less than 15 mm of tears. The smaller the number, the more severe the dry eye. A positive number change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Day 90

End point values	Carboxymethylcellulose Based Eye Drop Formulation A	OPTIVE UD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	198		
Units: mm/5 minutes				
arithmetic mean (standard deviation)				
Baseline (n=196,198)	9.29 (± 6.692)	8.1 (± 5.888)		
Change from Baseline at Day 90 (n=172,174)	1.38 (± 6.933)	1.53 (± 6.253)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 90 Days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	OPTIVE UD
Reporting group description:	
Carboxymethylcellulose Based Preservative-Free Lubricant Eye Drops (OPTIVE UD) 1-2 drops in each eye as needed at least 2 times daily for 90 days.	
Reporting group title	Carboxymethylcellulose Based Eye Drop Formulation A
Reporting group description:	
Carboxymethylcellulose Based Eye Drop Formulation A 1-2 drops in each eye as needed at least 2 times daily for 90 days.	

Serious adverse events	OPTIVE UD	Carboxymethylcellulose Based Eye Drop Formulation A	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 236 (1.69%)	5 / 224 (2.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Vitello-intestinal duct remnant			
subjects affected / exposed	1 / 236 (0.42%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial infarction			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 236 (0.42%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia	Additional description: Adverse Event male specific.		
subjects affected / exposed	1 / 236 (0.42%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	0 / 236 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OPTIVE UD	Carboxymethylcellulose Based Eye Drop Formulation A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 236 (2.54%)	15 / 224 (6.70%)	
Eye disorders			
Eye irritation			
subjects affected / exposed	6 / 236 (2.54%)	15 / 224 (6.70%)	
occurrences (all)	7	18	

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