Clinical trial results:
Double blind, randomized, multicenter, placebo-controlled, parallel-group design clinical trial of the efficacy and tolerability of cloriclomene hydrochloride capsules 100 mg TID in diabetic patients with mild to moderate non-proliferative retinopathy

Summary

EudraCT number	2004-002249-11
Trial protocol	IT
Global end of trial date	08 May 2009

Results information

Result version number	v1 (current)
This version publication date	28 August 2020
First version publication date	28 August 2020

Trial information

Trial identification

Sponsor protocol code	BLQ01-003-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bausch & Lomb Incorporated
Sponsor organisation address	1400 North Goodman Street, Rochester, United States, 14609
Public contact	Study Manager, Bausch&Lomb Dr Gerhard Mann chem.-Fabrik GmbH, natasa.orlic-pleyer@bausch.com
Scientific contact	Study Manager, Bausch&Lomb Dr Gerhard Mann chem.-Fabrik GmbH, Raphaele.SiouMermet@bausch.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 May 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2009
Global end of trial reached?	Yes
Global end of trial date	08 May 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the oral therapy with Cloricromene hydrochloride (Proendotel ®) capsules 100m admistered 3 time daily via oral route for 24 months, is superior to placebo in the arrest of progression of non-proliferative retinopathy in patients with diabetes of type I and II (insulin or non-insulin dependent)

Protection of trial subjects:

The protocol complied with the ethical principles for medical research and recommendations adopted by the 18th World Medical Assembly (Helsinki, 1964) and its amendments (52nd WMA General Assembly, Edinburgh, Scotland, October 2000, and clarifications by the WMA General Assembly, Washington 2002). The protocol also complied with the laws and regulations applicable in Italy. This study was conducted according to globally accepted standards of good clinical practice ed in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	21 April 2005
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	Italy: 127
Worldwide total number of subjects	127
EEA total number of subjects	127

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)	93
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients underwent an initial screening visit in which candidate patients for the study were selected, a 2- to 7-day run-in period, where patients had any non-permitted medications withdrawn prior to study entry and study entry criteria were checked, and a 24-month treatment period with the assigned study drug (active treatment).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ProEndotel

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cloricromene hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg via oral route. One capsule TID.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsules via oral route. One capsule TID.

Number of subjects in period 1	ProEndotel	Placebo
Started	62	65
Completed	30	31
Not completed	32	34
Consent withdrawn by subject	2	3
Physician decision	1	-

Adverse event, non-fatal	6	4
Other	3	2
Study Terminated by Sponsor	12	16
Lost to follow-up	1	5
Protocol deviation	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Phase
Reporting group description:	
ITT	

Reporting group values	Treatment Phase	Total	
Number of subjects	127	127	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	93	93	
From 65-84 years	34	34	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.0		
standard deviation	± 9.3	-	
Gender categorical Units: Subjects			
Female	48	48	
Male	79	79	

End points

End points reporting groups

Reporting group title	ProEndotel
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Patients with progression of retinopathy

End point title	Patients with progression of retinopathy[1]
End point description:	
End point type	Primary
End point timeframe:	
24 months	

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: Due to the low sample size reached and consequently the lack of statistical power, the statistical methods were modified to descriptive analysis for all endpoints and safety data.

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	39		
Units: Patients	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Best Corrected Visual Acuity (right eye)

End point title	Change from baseline in Best Corrected Visual Acuity (right eye)
End point description:	
End point type	Secondary
End point timeframe:	
24 months	

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	32		
Units: units				
least squares mean (standard error)	-0.009 (± 0.019)	-0.003 (± 0.021)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Best Corrected Visual Acuity (left)

End point title	Change from baseline in Best Corrected Visual Acuity (left)

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	31		
Units: units				
least squares mean (standard error)	-0.009 (± 0.023)	0.005 (± 0.025)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients with 3-line visual loss

End point title	Frequency of patients with 3-line visual loss

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	39		
Units: Patients	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of Macular Edema

End point title	Presence of Macular Edema

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: Patients	10	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean Retinal Thickness (right eye)

End point title	Change from baseline in mean Retinal Thickness (right eye)

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: units				
least squares mean (standard error)	8.217 (± 15.622)	20.101 (± 18.001)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean Retinal Thickness (left eye)

End point title	Change from baseline in mean Retinal Thickness (left eye)

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	ProEndotel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: units				
least squares mean (standard error)	7.598 (± 10.138)	28.430 (± 11.057)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	ProEndotel
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	ProEndotel	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 62 (11.29%)	2 / 65 (3.08%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm malignant			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			

subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ear and labyrinth disorders			
Otosalpingitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Labyrinthitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	ProEndotel	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 62 (9.68%)	5 / 65 (7.69%)	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 62 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 62 (3.23%)	1 / 65 (1.54%)	
occurrences (all)	2	1	

Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2 2 / 62 (3.23%) 2	0 / 65 (0.00%) 0 0 / 65 (0.00%) 0	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0	3 / 65 (4.62%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2004	Deletion of fluorescein angiography at visit 3 (month 6); Fluorescein angiography to be performed only in the most seriously affected eye, in case of bilateral affection; Centralized reading of fundus color photography, fluorescein angiography and OCT at AIBILI (Association for Innovation and Biomedical research on Light and Image) – Coimbra (Portugal); Best corrected visual acuity measured in both eyes at visit 1, and only in the affected eye in case of monolateral affection; demographic data to be collected in the run-in period Carton boxes were provided containing 40 blisters with 15 capsules each, instead of 60 blisters with 10 capsules each Specification that the interim analysis would be done "to assess consistency of progression rates in the Chloricromene and placebo groups with planned estimations"
27 September 2007	Change in selection criteria, to facilitate patients' enrolment: exclusion criterion "history of focal photocoagulation for diabetic macular edema in the study eye" modified as follows: "history of photocoagulation for diabetic macular edema in the study eye except focal photocoagulation at least 6 months before". This change had no impact on the primary end-point "progression of retinopathy"; Prolongation of the study timelines with study end postponed until December 2010, due to slow enrolment rate
30 November 2008	Anticipation of closure in study activities, due to slow enrolment rate, with study end established in May 2009.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the low sample size reached and consequently the lack of statistical power, the statistical methods were modified to descriptive analysis for all endpoints and safety data.

Notes: