Clinical trial results:
A Phase II trial comparing Brivudin 0.1% ophthalmic solution with Aciclovir 3 % ophthalmic ointment in the treatment of patients with herpetic dendritic keratitis

Summary

EudraCT number	2009-010971-26
Trial protocol	DE ES IT
Global end of trial date	26 October 2010

Results information

Result version number	v1 (current)
This version publication date	15 November 2018
First version publication date	15 November 2018

Trial information

Trial identification

Sponsor protocol code	2-BOPH

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A.
Sponsor organisation address	Via Sette Santi, 1, Florence, Italy, 50131
Public contact	Corporate Clinical Sciences, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it
Scientific contact	Corporate Clinical Sciences, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it

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	26 October 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2010
Global end of trial reached?	Yes
Global end of trial date	26 October 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

to compare the efficacy of brivudin 0.1% ophthalmic solution with aciclovir 3.0 % ophthalmic ointment in the healing (corneal re-epithelialisation) of herpetic dendritic keratitis.

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP would have affected the safety of the study participants, the Sponsor and the Investigator would have taken appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs would be informed forthwith about these new events and the measures taken. For patients participating in the study, Menarini Ricerche S.p.A. had stipulated an insurance policy in accordance with local regulatory requirements. Details on the insurance company, the insurance number and conditions were made available to patients in the ICF and/or provided as a separate document, in accordance with national requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	25
EEA total number of subjects	25

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	17
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After Screeening on Day 1 patients were randomized the same day to either the Brivudin or the Aciclovir arm of the study.

Period 1

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

Blinding implementation details:

Due to the obvious different appearance of the investigational product and the reference product (ophthalmic solution versus ophthalmic ointment), double-blind conditions could not be ascertained and, consequently, the study was conducted in an open-label fashion. However, a blinded assessment by Independent expert was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brivudin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Brivudin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Study medication (Brivudin 0.1% ophthalmic solution) had to be applied 5 times daily until healing of the corneal lesion was assessed by the Investigator. Thereafter, the study treatment had to be continued with the same posology for additional 7 days until the treatment termination visit.

Arm title	Aciclovir

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Aciclovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye ointment
Routes of administration	Ophthalmic use

Dosage and administration details:

Study medication (Aciclovir 3.0% ophthalmic ointment) had to be applied 5 times daily healing of the corneal lesion was assessed by the Investigator. Thereafter, the study treatment had to be continued with the same posology for additional 7 days until the treatment termination visit.

Number of subjects in period 1[1]	Brivudin	Aciclovir
Started	13	11
Completed	12	11
Not completed	1	0
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Reported data are from ITT population. One patient withdraw consent shortly after randomization and is not considered in the baseline number.

Baseline characteristics

Reporting groups	
Reporting group title	Brivudin
Reporting group description: -	
Reporting group title	Aciclovir
Reporting group description: -	

Reporting group values	Brivudin	Aciclovir	Total
Number of subjects	13	11	24
Age categorical Units: Subjects			
age 18 to 80 years	13	11	24
Age continuous Units: years			
arithmetic mean	49.3	56.6	
standard deviation	± 16.5	± 16.9	-
Gender categorical Units: Subjects			
Female	6	6	12
Male	7	5	12
Ophthalmoscopy unaffected eye Units: Subjects			
Normal	13	11	24
Abnormal	0	0	0
Ophthalmology affected eye Units: Subjects			
Normal	12	10	22
Abnormal	1	1	2
Visual Acuity Assessment unaffected eye Units: Subjects			
High/very high (20/10-20/16)	8	8	16
Normal/medium (>20/16 - >20/40)	5	3	8
Reduced (>20/40 - 20/63)	0	0	0
Severely reduced (>20/63)	0	0	0
Visual Aciuty Assessment affected eye Units: Subjects			
High/very high (20/10 - 20/16)	6	6	12
Normal/medium (>20/16 - >20/40)	7	4	11
Reduced (>20/40 - 20/63)	0	1	1
Severely reduced (>20/63)	0	0	0
Assessment of IOP affected eye - VALUE Units: Subjects			
Value <= 30 mmHg	13	11	24
Value > 30 mmHg	0	0	0
Assessment of IOP affected eye - METHOD used Units: Subjects			
Pneumatonometry	6	2	8

Rebound Tonometry	2	0	2
Palpation	5	9	14

IOP unaffected eye			
Goldman tonometry			
Units: mmHg			
arithmetic mean	15.2	14.3	
standard deviation	± 2.7	± 1.9	-

End points

End points reporting groups

Reporting group title	Brivudin
Reporting group description: -	
Reporting group title	Aciclovir
Reporting group description: -	

Primary: Time to healing

End point title	Time to healing[1]

End point description:

The primary efficacy variable was the time to healing of the herpetic corneal lesion (as assessed by the Independent Expert) in the ITT population. Healing was defined as re-epithelialisation of the cornea evidenced by the absence of fluorescein uptake in the area of the corneal lesion.

End point type	Primary

End point timeframe:

Evaluation period was approximately 14 days.

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 reduced sample size it was not possible to apply –as originally planned – a Cox Proportional Hazard Model for the calculation of the Hazard Ratio and the corresponding p-value. Results are therefore based on descriptive statistics.

End point values	Brivudin	Aciclovir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[2]	11		
Units: day				
arithmetic mean (standard deviation)	7.5 (± 2.7)	7.2 (± 3.5)		

Notes:

[2] - One patient randomised to Brivudin 0.1% did not provide any post-baseline efficacy assessment.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from first study treatment to one month after first study treatment.	
Adverse event reporting additional description:	
The safety population includes all patients screened receiving at least one study drug application.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	Brivudin
Reporting group description:	
Brivudin 0.1% five times daily for 7 days	
Reporting group title	Aciclovir
Reporting group description:	
Aciclovir 3.0% five times daily for 7 days	

Serious adverse events	Brivudin	Aciclovir	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Brivudin	Aciclovir	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	2 / 11 (18.18%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 14 (7.14%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
foreign body sensation in eyes			

subjects affected / exposed	2 / 14 (14.29%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	2 / 14 (14.29%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Eye pruritus			
subjects affected / exposed	1 / 14 (7.14%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Photophobia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Keratitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
keratitis herpetic			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

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