Clinical trial results:
A Phase I/II, Randomised, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy, Systemic Absorption and Dihydropyrimidine Dehydrogenase (DPD) Enzyme Activity Following Repeated Topical Applications of Brivudin Cream 0.5% and 1.0% in Patients with Herpes Simplex Labialis (HSL)

Summary

EudraCT number	2006-002213-13
Trial protocol	DE
Global end of trial date	03 December 2007

Results information

Result version number	v1 (current)
This version publication date	19 July 2019
First version publication date	19 July 2019

Trial information

Trial identification

Sponsor protocol code	6 BT

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
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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	03 December 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2007
Global end of trial reached?	Yes
Global end of trial date	03 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of this study is to investigate the efficacy of repeated topical applications of brivudin cream 0.5% and 1.0% versus placebo cream in the treatment of HSL as measured by the duration of the HSL episode, defined as time from start of treatment to:
a) Complete loss of hard crusts in classical HSL lesions.
b) Time to resolution of sign(s) and symptom(s) in aborted lesions (defined as lesions not developing beyond the papula stage).

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	18 October 2006
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	Germany: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	92
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 1 site in Germany. The first patient was enroled on 18 October 2006 and the last patient completed the study on 04 March 2007.

Pre-assignment

Screening details:

After screening on Day 1 patients were randomized the same day to either the Brivudin (0.5% cream or 1.0% cream) or placebo arm of the study in a 2:2:1 ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	0.5% Brivudin Cream

Arm description: -

Arm type	Experimental
Investigational medicinal product name	0.5% Brivudin Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

0.5 cm of 0.5% Brivudin cream applied twice daily from Day 1 to Day 3 and once in the morning of Day 4, using a standard spatula.

Arm title	1.0% Brivudin Cream

Arm description: -

Arm type	Experimental
Investigational medicinal product name	1.0% Brivudin Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

0.5 cm of 1.0% Brivudin cream applied twice daily from Day 1 to Day 3 and once in the morning of Day 4, using a standard spatula.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

0.5 cm of Placebo cream applied twice daily from Day 1 to Day 3 and once in the morning of Day 4, using a standard spatula.

Number of subjects in period 1	0.5% Brivudin Cream	1.0% Brivudin Cream	Placebo
Started	40	40	20
Completed	40	40	19
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	0.5% Brivudin Cream
Reporting group description: -	
Reporting group title	1.0% Brivudin Cream
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	0.5% Brivudin Cream	1.0% Brivudin Cream	Placebo
Number of subjects	40	40	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
85 years and over	0	0	0
Adults (18-84)	40	40	20
Age continuous Units: years			
arithmetic mean	40.4	38.0	35.8
standard deviation	± 12.5	± 15.6	± 9.8
Gender categorical Units: Subjects			
Female	32	26	13
Male	8	14	7

Reporting group values	Total		
Number of subjects	100		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
85 years and over	0		
Adults (18-84)	100		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	71		
Male	29		

End points

End points reporting groups	
Reporting group title	0.5% Brivudin Cream
Reporting group description: -	
Reporting group title	1.0% Brivudin Cream
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Duration of HSL lesion	
End point title	Duration of HSL lesion
End point description:	
End point type	Primary
End point timeframe:	
Daily evaluation up to Day 4. In case HSL symptomes had not resolved by Day 4, every other day until Day 14.	

End point values	0.5% Brivudin Cream	1.0% Brivudin Cream	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	40	20	
Units: day				
arithmetic mean (standard error)	4.5 (± 0.4)	3.8 (± 0.4)	3.9 (± 0.4)	

Statistical analyses

Statistical analysis title	Duration of HSL lesion
Statistical analysis description:	
Cox proportional hazards model with treatment and baseline lesion stage as covariates .	

Comparison groups	0.5% Brivudin Cream v 1.0% Brivudin Cream v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard

Notes:

[1] - A Hochberg procedure will be used to achieve an overall significance level of 5 % (two-sided).

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 (screening and first application) to Day 25 (Safety Follow Up)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups	
Reporting group title	0.5% Brivudin Cream
Reporting group description: -	
Reporting group title	1.0% Brivudin Cream
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	0.5% Brivudin Cream	1.0% Brivudin Cream	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	0.5% Brivudin Cream	1.0% Brivudin Cream	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 40 (50.00%)	16 / 40 (40.00%)	9 / 20 (45.00%)
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Facial neuralgia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Headache			

subjects affected / exposed	4 / 40 (10.00%)	5 / 40 (12.50%)	1 / 20 (5.00%)
occurrences (all)	4	5	2
Hypoaesthesia oral			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Paraesthesia oral			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Cheilitis			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	2 / 20 (10.00%)
occurrences (all)	0	2	2
Dry mouth			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Oral pruritus			

subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Oral pustule			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Ovulation pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)	3 / 40 (7.50%)	2 / 20 (10.00%)
occurrences (all)	2	3	2
Pharyngolaryngeal pain			
subjects affected / exposed	2 / 40 (5.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	6 / 40 (15.00%)	1 / 40 (2.50%)	3 / 20 (15.00%)
occurrences (all)	6	1	3
Night sweats			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pruritus generalised			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
skin laceration			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2006	Change of inclusion criterion 1: specification concerning women of childbearing potential Change of exclusion criterion 1: specification of "immunodeficient patients" Specification of prohibited concomitant medication: treatment with 5-FU forbidden within 4 weeks prior to the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported