Clinical trial results:
A multicentre, open-label, repeated-dose, pharmacokinetic study of Propranolol in infants treated for proliferating infantile hemangiomas (IHs) requiring systemic therapy.

Summary

EudraCT number	2009-018102-22
Trial protocol	FR
Global end of trial date	07 June 2011

Results information

Result version number	v1 (current)
This version publication date	17 February 2016
First version publication date	17 February 2016

Trial information

Trial identification

Sponsor protocol code	V00400SB102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Dermatologie
Sponsor organisation address	45, Place Abel Gance, Boulogne, France, 92100
Public contact	Medical and/or Clinical Study Manager , Pierre Fabre Dermatologie, contact_essais_cliniques@pierre-fabre.com
Scientific contact	Medical and/or Clinical Study Manager , Pierre Fabre Dermatologie, contact_essais_cliniques@pierre-fabre.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000511-PIP01-08
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	29 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2011
Global end of trial reached?	Yes
Global end of trial date	07 June 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to characterise the pharmacokinetics of propranolol (administered as an oral solution V0400 SB) at steady-state in infants during a treatment for proliferating infantile hemangiomas requiring systemic therapy.

Protection of trial subjects:

Clinical (including respiratory rate and vital sign measurements) and paraclinical (lab tests (haematology, biochemistry, glycaemia (pin-prick) and ECG) examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2010
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	France: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	23
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 23 patients who were included 10 were stratified to Group 1(infants aged from 35 to 90 days inclusive at inclusion), and 13 to Group 2(infants aged from 91 to 150 days inclusive at inclusion).

Pre-assignment

Screening details:

Infants 35 to 150 days of age with proliferating infantile hemangioma requiring sytemic therapy were stratified to 2 groups to their age at inclusion.

Period 1

Period 1 title	Propranolol hydrochloride oral solution (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 : 35 to 90 days

Arm description:

Infants aged from 35 to 90 days inclusive at inclusion
Repeated doses up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Propranolol hydrochloride oral solution
Investigational medicinal product code	V0400SB
Other name	Hemangiol
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Administration of propranolol oral solution twice daily.
Titration procedure :
D0: 1 mg/kg/day
D7: increase to 2 mg/kg/day
D14: increase to 3 mg/kg/day, up to the study end (Week 12).

Arm title	Group 2 : 91 to 150 days

Arm description:

Infants aged from 91 to 150 days inclusive at inclusion.
Repeated doses up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Propranolol hydrochloride oral solution
Investigational medicinal product code	V0400SB
Other name	Hemangiol
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Administration of propranolol oral solution twice daily.
Titration procedure :
D0: 1 mg/kg/day
D7: increase to 2 mg/kg/day
D14: increase to 3 mg/kg/day, up to the study end (Week 12).

Number of subjects in period 1	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days
Started	10	13
Completed	10	12
Not completed	0	1
Sponsor decision (increase QTcB on day 14-467ms)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 : 35 to 90 days
Reporting group description:	
Infants aged from 35 to 90 days inclusive at inclusion Repeated doses up to 12 weeks.	

Reporting group title	Group 2 : 91 to 150 days
Reporting group description:	
Infants aged from 91 to 150 days inclusive at inclusion. Repeated doses up to 12 weeks.	

Reporting group values	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days	Total
Number of subjects	10	13	23
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	10	13	23
Age continuous Units: days			
arithmetic mean	69.7	128.2	
full range (min-max)	50 to 89	91 to 152	-
Gender categorical Units: Subjects			
Female	7	10	17
Male	3	3	6

Subject analysis sets	
Subject analysis set title	Safety/efficacy set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients treated (safety set) with at least one post-baseline efficacy assessment (efficacy set).	
Subject analysis set title	PK set Group 1
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients having taken all study medications and not presenting any major deviation (for PK evaluation).	
Subject analysis set title	Pk set Group 2
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients having taken all study medications and not presenting any major deviation (for PK evaluation)	

Reporting group values	Safety/efficacy set	PK set Group 1	Pk set Group 2
Number of subjects	23	8	11
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	23	8	11

Age continuous Units: days			
arithmetic mean	102.7	69.3	134.5
full range (min-max)	50 to 152	50 to 89	113 to 152
Gender categorical Units: Subjects			
Female	17	5	8
Male	6	3	3

End points

End points reporting groups

Reporting group title	Group 1 : 35 to 90 days

Reporting group description:

Infants aged from 35 to 90 days inclusive at inclusion
Repeated doses up to 12 weeks.

Reporting group title	Group 2 : 91 to 150 days

Reporting group description:

Infants aged from 91 to 150 days inclusive at inclusion.
Repeated doses up to 12 weeks.

Subject analysis set title	Safety/efficacy set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients treated (safety set) with at least one post-baseline efficacy assessment (efficacy set).

Subject analysis set title	PK set Group 1
Subject analysis set type	Per protocol

Subject analysis set description:

Patients having taken all study medications and not presenting any major deviation (for PK evaluation).

Subject analysis set title	Pk set Group 2
Subject analysis set type	Per protocol

Subject analysis set description:

Patients having taken all study medications and not presenting any major deviation (for PK evaluation)

Primary: Propranolol - Maximum plasma concentration (Cmax) -

End point title	Propranolol - Maximum plasma concentration (Cmax) -[1]

End point description:

End point type	Primary

End point timeframe:

Steady-state PK parameters after repeated twice daily oral administration of propranolol (3 mg/kg/day) for 2 weeks (Group 1) and for 10 weeks (Group2)(following a 2-week uptitration in both groups).
6 micro-blood samples were collected over 9 hours.

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: Descriptive analyses were performed based on the study groups.

End point values	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: ng/mL				
geometric mean (full range (min-max))	78.5 (47.8 to 119)	79.2 (21.3 to 448)		

Statistical analyses

No statistical analyses for this end point

Primary: Propranolol - Area under the plasma concentration time curve observed between two administrations (AUCτ) -

End point title	Propranolol - Area under the plasma concentration time curve observed between two administrations (AUCτ) -[2]

End point description:

End point type	Primary

End point timeframe:

Steady-state PK parameters after repeated twice daily oral administration of propranolol (3 mg/kg/day) for 2 weeks (Group 1) and for 10 weeks (Group2)(following a 2-week uptitration in both groups).
6 micro-blood samples were collected over 9 hours.

Notes:

[2] - 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: Descriptive analyses were performed based on the study groups.

End point values	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: h.ng/mL				
geometric mean (full range (min-max))	541 (360 to 804)	430 (116 to 1193)		

Statistical analyses

No statistical analyses for this end point

Primary: Propranolol - Time to reach the maximum plasma concentration (Tmax) -

End point title	Propranolol - Time to reach the maximum plasma concentration (Tmax) -[3]

End point description:

End point type	Primary

End point timeframe:

Steady-state PK parameters after repeated twice daily oral administration of propranolol (3 mg/kg/day) for 2 weeks (Group 1) and for 10 weeks (Group2)(following a 2-week uptitration in both groups).
6 micro-blood samples were collected over 9 hours.

Notes:

[3] - 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: Descriptive analyses were performed based on the study groups.

End point values	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: hour				
median (full range (min-max))	2 (1 to 9)	2 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Primary: Propranolol - oral clearance (Cltot/F/kg) -

End point title	Propranolol - oral clearance (Cltot/F/kg) -[4]

End point description:

End point type	Primary

End point timeframe:

Steady-state PK parameters after repeated twice daily oral administration of propranolol (3 mg/kg/day) for 2 weeks (Group 1) and for 10 weeks (Group2)(following a 2-week uptitration in both groups).
6 micro-blood samples were collected over 9 hours.

Notes:

[4] - 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: Descriptive analyses were performed based on the study groups.

End point values	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: L/h/kg				
geometric mean (full range (min-max))	2.71 (1.84 to 4.05)	3.27 (1.18 to 12.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Whole Study Period

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Group 1 : 35 to 90 days

Reporting group description:

Infants aged from 35 to 90 days inclusive at inclusion
Repeated doses up to 12 weeks.

Reporting group title	Group 2 : 91 to 150 days

Reporting group description:

Infants aged from 91 days to 150 inclusive at inclusion.
Repeated doses up to 12 weeks.

Serious adverse events	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Crying			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
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: 5 %

Non-serious adverse events	Group 1 : 35 to 90 days	Group 2 : 91 to 150 days	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	12 / 13 (92.31%)	
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	3 / 10 (30.00%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	4 / 13 (30.77%)	
occurrences (all)	5	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 10 (10.00%)	3 / 13 (23.08%)	
occurrences (all)	2	4	
Psychiatric disorders			
Nightmare			
subjects affected / exposed	3 / 10 (30.00%)	4 / 13 (30.77%)	
occurrences (all)	3	4	
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood alkaline phosphatase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood potassium increased			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Poor quality sleep			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 10 (30.00%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	5 / 13 (38.46%)	
occurrences (all)	2	8	
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

Teething			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 10 (30.00%)	3 / 13 (23.08%)	
occurrences (all)	4	3	
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infected bites			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tracheitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Varicella			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 10 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2010	- Increase of the sample size from 18 to 20 infants (EMA requirement) – Precision on the ECG assessment (added by the Sponsor) – Addition of the quantification of the 4-OH-propranolol (the metabolite of propranolol) in order to complete the PK profile (added by the Sponsor)
01 July 2010	– Change of the Study Medical Manager – Change of Sponsor representative's address – Annual update of the Investigator Brochure (addition of new bibliographical references, addition of compassionate use experience with the product)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported